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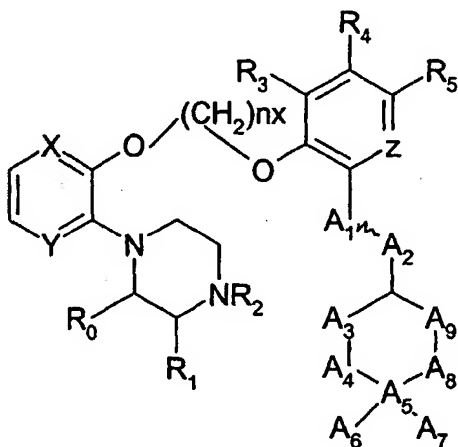
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(54) Title: NOVEL COMPOUNDS, THEIR USE AND PREPARATION



(I)

(57) Abstract: The invention relates to compounds of the general Formula (I). The compounds may be prepared by per se conventional methods and can be used for treating a human or animal subject suffering from a serotonin-related disorder. The invention also relates to such use as well as to pharmaceutical compositions comprising a compound of Formula (I).

NOVEL COMPOUNDS, THEIR USE AND PREPARATION**Related applications**

This application claims priority to Swedish application number 0201881-0, filed on
5 June 19, 2002, Swedish application number 0202516-1, filed on August 26, 2002, U.S.
provisional application 60/406,119, filed on August 26, 2002, and U.S. provisional
application 60/416,701, filed on October 7, 2002, the contents of which are incorporated
herein by reference.

Field of the invention

10 The present invention relates to novel compounds, to pharmaceutical compositions
comprising the compounds, to processes for their preparation, as well as to the use of the
compounds for the preparation of a medicament which particularly acts on the central nervous
system.

Background of the invention

15 Many disorders and conditions of the central nervous system are influenced by the
adrenergic, the dopaminergic, and the serotonergic neurotransmitter systems. For example,
serotonin has been implicated in a number of disorders and conditions which originate in the
20 central nervous system. A number of pharmacological and genetic experiments involving
receptors for serotonin strongly implicate the 5-HT_{2C} receptor subtype in the regulation of
food intake (see e. g., *Obes. Res.* 1995, 3, Suppl. 4, 449S-462S, *Diabetes, Obesity and
Metabolism* 1999, 1, 207-214, and *Drugs Future* 2001, 26, 383-393). The 5-HT_{2C} receptor
subtype is transcribed and expressed in hypothalamic structures associated with appetite
25 regulation. It has been demonstrated that the 5-HT_{2C} receptor agonist *m*-chlorophenyl-
piperazine (mCPP), which has some preference for the 5-HT_{2C} receptor, reduces food intake
in mice that express the normal 5-HT_{2C} receptor while the compound lacks activity in mice
expressing the mutated inactive form of the 5-HT_{2C} receptor (*Nature* 1995, 374, 542-546). In
a recent clinical study, a slight but sustained reduction in body weight was obtained after 2
30 weeks of treatment with mCPP in obese subjects (*Psychopharmacology* 1997, 133, 309-312).
Recently, a series of pyrrolo[3,2,1-*ij*]quinoline derivatives was identified to be 5-HT_{2C}
receptor agonists having selectivity over the 5-HT_{2A} receptor (Isaac M., et al., *Bioorg. Med.*

Chem. Lett. 2000, 10, 919-921). The compounds are said to offer a novel approach to the treatment of obesity and epilepsy.

Body weight reduction has also been reported from clinical studies with other "serotonergic" agents (see e.g. IDrugs 1998, 1, 456-470). For example, the 5-HT reuptake inhibitor fluoxetine and the 5-HT releasing agent/reuptake inhibitor dexfenfluramine have exhibited weight reduction in controlled studies. However, currently available drugs that increase serotonergic transmission appear to have only a moderate and, in some cases, transient effects on the body weight.

The 5-HT_{2C} receptor subtype has also been suggested to be involved in CNS disorders such as depression and anxiety (Exp. Opin. Invest. Drugs 1998, 7, 1587-1599; IDrugs, 1999, 2, 109-120).

The 5-HT_{2C} receptor subtype has further been suggested to be involved in urinary disorders such as urinary incontinence (IDrugs, 1999, 2, 109-120).

Compounds which have a selective effect on the 5-HT_{2C} receptor may therefore have a therapeutic potential in the treatment of disorders like those mentioned above. Of course, selectivity also reduces the potential for adverse effects mediated by other serotonin receptors.

Information disclosure

US-A-3,253,989 discloses the use of mCPP as an anorectic agent.

EP-A1-863 136 discloses azetidine and pyrrolidine derivatives which are selective 5-HT_{2C} receptor agonists having antidepressant activity and which can be used for treating or preventing serotonin-related diseases, including eating disorders and anxiety.

EP-A-657 426 discloses tricyclic pyrrole derivatives having activity on the 5-HT_{2C} receptor and which inter alia may be used for treating eating disorders.

EP-A-655 440 discloses 1-aminoethylindoles having activity on the 5-HT_{2C} receptor and which may be used for treating eating disorders.

EP-A-572 863 discloses pyrazinoindoles having activity on the 5-HT_{2C} receptor and which may be used for treating eating disorders.

J. Med. Chem. 1978, 21, 536-542 and US-A-4,081,542 disclose a series of piperazinyipyrazines having central serotonin-mimetic activity. In particular, US-A-4,081,542 discloses such compounds as anorectic agents.

J. Med. Chem. 1981, 24, 93-101 discloses a series of piperazinyloinoxalines with central serotonin-mimetic activity.

WO 00/12475 discloses indoline derivatives as 5-HT_{2B} and/or 5-HT_{2C} receptor ligands, especially for the treatment of obesity.

WO 00/12510 discloses pyrroloindoles, pyridoindoles and azepinoindoles as 5-HT_{2C} receptor agonists, particularly for the treatment of obesity.

5 WO 00/12482 discloses indazole derivatives as selective, directly active 5-HT_{2C} receptor ligands, preferably 5-HT_{2C} receptor agonists, particularly for use as anti-obesity agents.

WO 00/12502 discloses pyrroloquinolines as 5-HT_{2C} receptor agonists, particularly for use as anti-obesity agents.

10 GB-B-1,457,005 discloses 1-piperazinyl-2-[2-(phenyl)ethenyl]-quinoxaline derivatives which exhibit anti-inflammatory activity.

Chem. Pharm. Bull. 1993, 41(10) 1832-1841 discloses 5-HT₃ antagonists including 2-(4-methyl-1-piperazinyl)-4-phenoxyquinoxaline.

15 GB-B-1,440,722 discloses 2-(1'-piperazinyl)-quinoxaline compounds having pharmaceutical activity against depression.

WO 96/11920 discloses CNS-active pyridinylurea derivatives.

WO 95/01976 discloses indoline derivatives active as 5-HT_{2C} antagonists and of potential use in the treatment of CNS disorders.

20 WO 97/14689 discloses aryl-piperazine cyclic amine derivatives which are selective 5-HT_{1D} receptor antagonists.

WO 98/42692 discloses piperazines derived from cyclic amines which are selective antagonists of human 5-HT_{1A}, 5-HT_{1D} and 5-HT_{1B} receptors.

GB-B-1,465,946 discloses substituted pyridazinyl, pyrimidinyl, pyrazinyl and pyridyl compounds which are active as β -receptor blocking agents.

25 EP-A-711757 discloses [3-(4-phenyl-piperazin-1-yl)propylamino]-pyridine, pyrimidine and benzene derivatives as α -adrenoceptor antagonists.

WO 99/03833 discloses aryl-piperazine derivatives which are 5-HT₂ antagonists and 5-HT_{1A} receptor agonists and therefore are useful as remedies or preventives for psychoneurosis.

30 WO 96/02525 discloses aryl-piperazine-derived piperazide derivatives having 5-HT receptor antagonistic activity.

WO 99/58490 discloses aryl-hydronaphthalen-alkanamines which may effectuate partial or complete blockage of serotonergic 5-HT_{2C} receptors in an organism.

WO 00/35922 discloses 2,3,4,4a-tetrahydro-1H-pyrazino[1,2-a]quinoxalin-5(6H)ones as 5-HT_{2C} agonists, which may be used for the treatment of obesity.

5 WO 00/44737 discloses aminoalkylbenzofurans as 5-HT_{2C} agonists, which may be used for the treatment of obesity.

Further compounds reported to be 5-HT_{2C} receptor agonists are, for example, indazolylpropylamines of the type described in WO 00/12481; indazoles of the type described in WO 00/17170; piperazinyipyrazines of the type described in WO 00/76984, WO 02/40456 and WO 02/40457; heterocycle fused γ -carboline of the type described in WO 00/77001, WO 00/77002 and WO 00/77010; benzofuryl piperazines of the type described in WO 01/09111 and WO 01/09123; benzofurans of the type described in WO 01/09122; benzothiophenes of the type described in WO 01/09126; aminoalkylindazoles of the type described in WO 98/30548; indoles of the type described in WO 01/12603; indolines of the type described in WO 15 01/12602 and WO 02/44152; pyrazino(aza)indoles of the type described in WO 00/44753; diaza-cyclopenta[a]indenes of the type described in EP 1132389; piperazine derivatives of the type described in WO 02/10169; quinoxalinones of the type described in US 6372745, and tricyclic pyrroles or pyrazoles of the type described in WO 98/56768.

WO 98/33504 discloses a new medical use of 1-[6-chloro-5-(trifluoromethyl)-2-pyridinyl]piperazine, in particular to a new method of treating urinary incontinence.

WO 02/36596 discloses cycloalkyl[b][1,4]-diazepino[6,7-hi]indoles as serotonin 5-HT_{2C} receptor agonists, which may be used for the treatment of obesity.

WO 03/00666 discloses [1,2']bipyrazinyl 5-HT₂ receptor ligands, in particular 5-HT_{2C} receptor ligands, for treatment of sexual dysfunction.

25 WO 03/00663 discloses piperazinyipyrimidines as 5-HT₂ receptor ligands, in particular 5-HT_{2C} receptor ligands, for treatment of sexual disorders.

WO 02/51844 discloses cycloalkyl fused indole derivatives and their use as 5-HT_{2b} and 5-HT_{2C} receptor ligands.

WO 02/42304 discloses cyclopenta[b][1,4]diazepino[6,7,1-hi]indoles as selective 5-HT_{2C} receptor agonists.

30 WO 02/36596 discloses diazepinocarbazoles and related compounds as serotonin 5-HT_{2C} agonists.

WO 02/48124 discloses piperazine derivatives as 5-HT_{2C} receptor agonists, which may be used for, e.g., obesity.

WO 01/66548 discloses azaindolyl derivatives as 5-HT_{2b} and 5-HT_{2c} receptor ligands, preferably 5-HT_{2c} receptor agonists, for use in therapy, especially for use as anti-
5 obesity agents.

WO 02/072584 discloses tetrahydropyrazinoindoles as 5-HT_{2b} and 5-HT_{2c} receptor ligands, preferably 5-HT_{2c} receptor agonists, for use in therapy, especially for use as anti-obesity agents.

WO 00/76984 and WO 02/40457 disclose aryl-piperazine derivatives which bind to
10 the 5-HT_{2C} receptor (agonists and antagonists) useful for the treatment of serotonin-related disorders. However, the 5-HT_{2C} receptor selectivity of the compounds according to the present invention is unexpectedly high compared to the compounds according to WO 00/76984 and WO 02/40457.

The absence of appreciable affinity to certain other 5-HT receptor subtypes may
15 provide the basis for an improved therapeutic index compared with the general activation of all the different 5-HT receptor subtypes by 5-HT reuptake inhibitors and/or 5-HT releasing agents. The anti-obesity drug dexfenfluramine, a 5-HT reuptake inhibitor and 5-HT releaser, was withdrawn from the market in September 1997 because of several reports suggesting the association of this drug with a risk of primary pulmonary hypertension and of heart valve
20 abnormalities (see, e.g. Kolanowski, J. A risk-benefit assessment of anti-obesity drugs. Drug Safety 1999, 20, 119-131). The 5-HT/noradrenaline reuptake inhibitor sibutramine, currently on the market for the treatment of obesity, can increase blood pressure and heart rate in some patients. The use of sibutramine has been suspended in Italy in March 2002 because of two cardiovascular deaths and its safety is currently under review in other European countries
25 where, in the UK and France alone, there have been a total of 103 serious adverse reaction reports in people using the drug including two deaths in Britain. Taken together, there is a need for the development of safer anti-obesity agents.

It is important to minimize potential adverse events due to activation of 5-HT_{2A} and 5-HT_{2B} receptor subtypes. 5-HT_{2A} receptor agonism is associated with vasoconstriction,
30 platelet aggregation and hallucinogenic episodes and 5-HT_{2B} receptor agonism might play a role in the pathophysiology of migraine. Stimulation of 5-HT_{2A} and 5-HT_{2B} receptors might also have a link to cardiac fibrosis.

The following references show that hallucinogenic effects are associated with activation of the 5-HT_{2A} receptor:

- (a) Glennon, R.A. et al. Hallucinogens and Serotonergic Mechanisms. NIDA Res. Mongr. 1992, 119P, 131-135.
- 5 (b) Egan, C.T. et al. Agonist Activity of LSD and Lisuride at cloned 5-HT_{2A} and 5-HT_{2C} receptors. Psychopharmacol. 1998, 136, 409-414.
- (c) Roth, B.L. et al. The multiplicity of serotonin receptors: Uselessly diverse molecules or an embarrassment of riches? Neuroscientist 2000, 6, 252-262.
- (d) Arvanov, V.L. et al. LSD and DOB: interaction with 5-HT_{2A} receptors to inhibit NMDA
10 receptor-mediated transmission in the rat prefrontal cortex. Eur. J. Neurosci. 1999, 11, 3064-3072.
- (e) Marek, G.J. et al. LSD and the phenethylamine hallucinogen DOI are potent partial agonists at 5-HT_{2A} receptors on interneurons in rat piriform cortex. J. Pharmacol. Exp. Ther. 1996, 278, 1373-1382.
- 15 (f) Roth, B.L. et al. Activation is hallucinogenic and antagonism is therapeutic: role of 5-HT_{2A} receptors in atypical antipsychotic drug actions. Neuroscientist 1999, 5, 254-262.
- (g) Aghajanian, G.K. et al. Serotonin and Hallucinogens. Neuropsychopharmacology 1999, 21, 16S-23S.
- (h) Aghajanian, G.K. et al. Serotonin model of schizophrenia: emerging role of glutamate
20 mechanisms. Brain Res. Rev. 2000, 31, 302-312.

The following references show that vasoconstrictive effects are associated with activation of the 5-HT_{2A} receptor:

- (a) Roth, B.L. et al. 5-HT₂-family receptors (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}): where structure meets function. Pharmacol. Ther. 1998, 79, 231-257.
- 25 (b) Florian, J.A. et al. Integration of mitogen-activated protein kinase activation in vascular 5-hydroxytryptamine 2A receptor signal transduction. J. Pharmacol. Exp. Ther. 1998, 284, 346-355.
- (c) Saxena, P.R. Serotonin receptors: Subtypes, functional responses and therapeutic relevance. Pharmacol. Ther. 1995, 66, 339-368.
- 30 (d) MacLennan, S.J. 5-HT receptors in the human cardiovascular system. ID Res. Alert 1997, 2, 207-213.
- (e) Nilsson, T. et al. Characterisation of 5-HT receptors in human coronary arteries by molecular and pharmacological techniques. Eur. J. Pharmacol. 1999, 372, 49-56.

(f) MacLean, M.R. et al. 5-Hydroxytryptamine receptors mediating vasoconstriction in pulmonary arteries from control and pulmonary hypertensive rats. *Br. J. Pharmacol.* 1996, 119, 917-930.

(g) Cortijo, J. et al. Characterization of 5-HT receptors on human pulmonary artery and vein: functional and binding studies. *Br. J. Pharmacol.* 1997, 122, 1455-1463.

(h) O'Connor, S.E. et al. Cardiovascular effects of SL65.0472, a 5-HT receptor antagonist. *Eur. J. Pharmacol.* 2001, 414, 259-269.

(i) Galzin, A.-M. et al. Effects of SL 65.0472, a novel 5-HT receptor antagonist, on 5-HT receptor mediated vascular contraction. *Eur. J. Pharmacol.* 2000, 404, 361-368.

The following references show that 5-HT_{2A} agonism is associated with platelet aggregation, thrombosis and atherosclerosis:

(a) Li, N. et al. Effects of serotonin on platelet activation in whole blood. *Blood Coagul Fibrinolysis* 1997, 8, 517-523.

(b) Takano, S. Role of 5-hydroxytryptamine in platelet thrombus formation and mechanisms of inhibition of thrombus formation by 5-hydroxytryptamine 2A antagonists in rabbits. *Arch. Int. Pharmacodyn. Ther.* 1995, 330, 297-308.

(c) de Clerck, F. The role of serotonin in thrombogenesis. *Clin. Physiol. Biochem.* 1990, 8 (Suppl. 3), 40-49.

One of the initiating events of atherosclerosis is endothelial injury followed by platelet aggregation. During atherosclerosis, platelets aggregate more readily and greater quantities of serotonin are released from platelets. Vascular responses to serotonin released by activated platelets are profoundly altered in a direction that favours vasoconstriction (arterial spasm), which ultimately may lead to thrombosis and complete obstruction of the vessel. Vascular smooth muscle cell proliferation is believed to play an important role in the pathogenesis of atherosclerosis. Serotonin is known to be a mitogen for vascular smooth muscle cells by stimulation of the 5-HT_{2A} receptor [tentatively via activation of MAPK (mitogen-activated protein kinase) and/or PKC (protein kinase C) dependent pathways], see:

(a) Lee, S.-L. et al. Serotonin stimulates mitogen-activated protein kinase activity through the formation of superoxide anion. *Am. J. Physiol.* 1999, 277, (2Pt.1), L-282-L291.

(b) Florian, J.A. et al. Integration of mitogen-activated protein kinase activation in vascular 5-hydroxytryptamine_{2A} receptor signal transduction. *J. Pharmacol. Exp. Ther.* 1998, 284, 346-355.

(c) Banes A. et al. Mechanisms of 5-hydroxytryptamine_{2A} receptor activation of the mitogen-activated protein kinase pathway in vascular smooth muscle. J. Pharmacol. Exp. Ther. 1999, 291, 1179-1187.

(d) Watanabe, T. et al. Lipid peroxidation product 4-hydroxy-2-nonenal acts synergistically with serotonin in inducing vascular smooth muscle cell proliferation. Atherosclerosis 2001, 155, 37-44.

(e) Pakala, R. et al. Eicosapentaenoic Acid and Docosahexaenoic Acid Block Serotonin-Induced Smooth Muscle Cell Proliferation. Atheroscler. Thromb. Vasc. Biol. 1999, 19, 2316-2322.

10 Furthermore, it has been suggested that increased vasoconstrictor response to 5-HT in atherosclerotic vessels might be due to supersensitive 5-HT_{2A} receptors, see: Fujiwara, T. et al. Augmented responses to 5-HT₂-receptor-mediated vasoconstrictions in atherosclerotic rabbit common carotid arteries. J. Cardiovasc. Pharmacol. 1995, 26, 503-510.

A 5-HT-induced upregulation of thrombin receptor expression in vascular smooth muscle cells, via activation of 5-HT_{2A} receptors, has also been implicated to play a role in atherosclerosis, see: Schini-Kerth V.B. et al. Serotonin stimulates the expression of thrombin receptors in cultured vascular smooth muscle cells. Role of protein kinase C and protein tyrosine kinases. Circulation 1996, 93, 2170-2177.

The following references show that 5-HT_{2B} agonism is associated with migraine:

20 (a) Schmuck, K. et al. Activation of meningeal 5-HT_{2B} receptors: an early step in the generation of migraine headache. Eur. J. Neurosci. 1996, 8, 959-967.

(b) Johnson, K.W. et al. Serotonin in migraine: Theories, animal models and emerging therapies. Prog. Drug. Res. 1998, 51, 219-244.

(c) Parsons, A.A. Prophylaxis of migraine. Curr. Opin. CPNS Invest. Drugs 2000, 2, 160-166.

25 The following reference show that pulmonary hypertension is associated with activation of the 5-HT_{2B} receptor:

(a) Launay, J.-M. et al. Function of the serotonin 5-hydroxytryptamine 2B receptor in pulmonary hypertension. Nature Med. 2002, 8, 1129-1135.

The following references show that 5-HT_{2A} and especially 5-HT_{2B} agonism is associated with the origin of cardiac fibrosis after treatment with marketed anti-obesity preparations such as dexfenfluramin:

30

(a) Rothman, R.B. et al. Evidence for possible involvement of 5-HT_{2B} receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. *Circulation* 2000, 102, 2836-2841.

(b) Fitzgerald, L.W. et al. Possible role of valvular serotonin 5-HT_{2B} receptors in the

5 cardiopathy associated with fenfluramine. *Mol. Pharmacol.* 2000, 57, 75-81.

(c) Setola, V. et al. 3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy") induces fenfluramine-like proliferative actions on human cardiac valvular interstitial cells in vitro. *Mol. Pharmacol.* 2003, 63, 1223-1229.

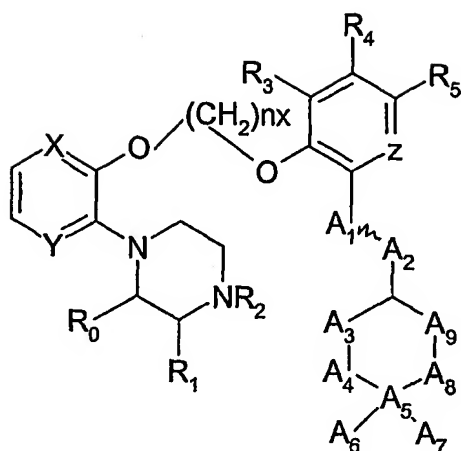
As denoted below, the present compounds may be used in order to treat serotonin-related conditions such as menopausal and post-menopausal hot flushes. Berendsen H.H.G. "Hot flushes and serotonin". *Journal of the British Menopause Society*. 2002, 8, 30-34, indicates that non-hormonal treatment with either 5-HT_{2A} receptor antagonists or 5-HT_{2C} receptor agonists may have several advantages over hormonal therapy.

Another example of serotonin-related disorders is weight gain associated with antipsychotic drug administration. WO 02/19998 discloses that the use of atypical antipsychotic agents is associated with weight gain in up to 50% of patients, a significant portion of the patient population. Piesla, M.J. et al. Atypical antipsychotic-like effects of 5-HT_{2C} agonists. *Schizophrenia Res.* 2001, 49 (1-2; Sp Iss, Suppl.) 95, discloses that 5-HT_{2C} agonists have anti-psychotic potential. Therefore, therapy using 5-HT_{2C} agonists will probably counteract an increase in body weight induced by antipsychotic drugs without counteracting the antipsychotic effect. It is reasonable to expect that the antipsychotic effect will be strengthened.

Summary of the invention

According to the present invention, a class of novel compounds have been developed which bind to the 5-HT_{2C} receptor, which compounds may be agonists, partial agonists or antagonists for this receptor, preferably agonists or partial agonists. Therefore, the present compounds may be used for the treatment of serotonin-related disorders and conditions. Furthermore, it has been shown that the 5-HT_{2C} receptor selectivity of the present compounds is unexpectedly high compared to prior art compounds.

In one aspect, the invention provides novel compounds of the general Formula (I):



Formula (I)

wherein

5 nx is 2-4, preferably 2;

R_0 and R_1 are each independently H or CH_3 ;

R_2 is H, C_1 - C_4 -alkyl, 2-hydroxyethyl, 2-cyanoethyl or tetrahydropyran-2-yl, C_1 - C_4 -acyl or C_1 - C_4 -alkoxycarbonyl;

10 R_3 - R_5 are each independently H, halogen, methyl or methoxy, provided that at least one of R_3 - R_5 is hydrogen;

X, Y, and Z are each independently CH or N;

A_1 is O, CH or CH_2 ;

A_2 is O, CH or $(CH_2)_{n2}$, wherein $n2$ is an integer 0-2;

the bond between A_1 and A_2 is a single or double bond;

15 A_3 is $(CH_2)_{n3}$, wherein $n3$ an integer 0-10, preferably 0-7, more preferably 0-5;

A_4 is $(CMe_2)_{n4}$, wherein $n4$ is an integer 0-1;

A_5 is N or O;

20 A_6 and A_7 are each independently H, C_1 - C_4 -alkyl, amino- C_2 - C_4 -alkyl, N,N-di- C_1 - C_4 -alkylamino- C_2 - C_4 -alkyl, C_3 - C_6 -cycloalkyl or form together with A_5 a saturated heterocyclic ring;

A_8 is $(CH_2)_{n8}$, wherein $n8$ is an integer 0-2;

A_9 is H or CH_2 ;

or pharmaceutically acceptable salts, solvates, hydrates, geometrical isomers, tautomers, optical isomers, N-oxides and prodrug forms thereof;

25 provided that when A_5 is N, then A_5 is substituted by only two of A_6 , A_7 and A_8 ; when A_5 is O, then A_5 is substituted by only one of A_6 , A_7 and A_8 .

In case the compounds of Formula (I) can be in the form of optical isomers, the invention comprises the racemic mixture as well as the individual enantiomers as such.

In other aspects, the compounds of formula (I) are those wherein:

In case at least one of the integers n_2 , n_3 , n_4 or n_8 referred to above equals 0, then the corresponding group A_2 , A_3 , A_4 or A_8 equals a single bond. However, in the case when A_9 equals H, then A_8 does not equal a single bond between A_5 and A_9 . In the case when n_8 equals 1 or 2, then A_5 is not substituted by A_7 .

When A_1 is CH_2 , A_2 is O and A_5 is N, then both n_3 and n_4 are not 0.

When one of A_1 and A_2 is O, the other of A_1 and A_2 may not be O.

When one of A_1 and A_2 is CH, then the other of A_1 and A_2 is also CH, wherein the bond between A_1 and A_2 is a double bond.

When A_5 is O, then A_5 is not substituted by A_7 and A_8 , and A_9 represents H and A_6 is amino- C_2 - C_4 -alkyl or N,N-di- C_1 - C_4 -alkylamino- C_2 - C_4 -alkyl, and further n_3 and n_4 are preferably both 0.

When A_3 , A_4 , A_5 , A_8 and A_9 together with the carbon atom between A_3 and A_9 form a 4-7 membered saturated heterocyclic ring (e.g. azacyclic ring), then A_9 is CH_2 , n_4 is 0, and the sum of $n_3 + n_8$ is an integer 1-4.

When A_9 is CH_2 , then all of n_3 , n_4 , and n_8 are not 0.

When A_9 is CH_2 and A_5 is N, then n_4 is 0. When n_4 is 1, then A_9 is preferably H and A_5 is preferably N.

When A_5 is nitrogen, the A_6 and A_7 are each independently H, C_1 - C_4 -alkyl, C_3 - C_6 -cycloalkyl or form together a saturated heterocyclic ring.

In case R_0 is methyl, it is preferred that the carbon atom, to which the said methyl group R_0 is attached, is in the (*R*)-configuration.

It is preferred that R_1 is hydrogen.

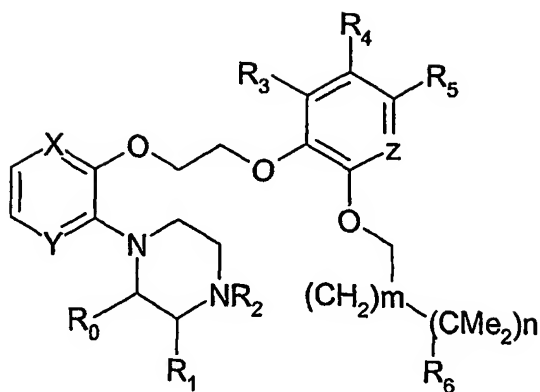
It is also preferred that X and Y both are nitrogen.

It is also preferred that R_2 is H or methyl.

It is also preferred that all of R_3 - R_5 are H.

It is also preferred that A_6 and A_7 are each independently H, methyl, isopropyl, 2-ethylamine or form together with A_5 a pyrrolidine or piperazine ring.

In one preferred embodiment, the invention refers to a compound of Formula (Ia):



Formula (Ia)

wherein:

5 R_0 - R_5 , X, Y, and Z are as defined above, preferably wherein Z is N,

m is an integer 0-10, preferably 0-7, more preferably 0-5,

n is an integer 0 or 1, wherein the sum of m + n is preferably at least 1,

R_6 is NR_7R_8 or OR_9 , wherein

R_7 and R_8 are each independently H or straight or branched C_1 - C_4 -alkyl;

10 or R_7 and R_8 form together with the nitrogen atom to which they are attached a saturated heterocyclic ring;

R_9 is amino- C_2 - C_4 -alkyl or N,N-di- C_1 - C_4 -alkylamino- C_2 - C_4 -alkyl.

It is preferred that R_7 and R_8 are selected from H, methyl, isopropyl, or form together with the nitrogen atom to which they are attached a pyrrolidine or

15 piperazine ring. It is also preferred that R_9 is 2-aminoethyl.

Specific compounds of Formula (Ia) are:

N,N-Dimethyl-(2-(3-[2-(2-(*R*)-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrazinyl-3'-yloxy)-ethoxy]-pyridin-2-yloxy)-ethyl)-amine;

20 *N,N*-Diisopropyl-(2-(3-[2-(2-(*R*)-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrazinyl-3'-yloxy)-ethoxy]-pyridin-2-yloxy)-ethyl)-amine;

N,N-Dimethyl-2-[(3-{2-[(3-piperazin-1-ylpyrazin-2-yl)oxy]ethoxy}pyridin-2-yl)oxy]ethanamine;

2-[(2*R*)-2-Methylpiperazin-1-yl]-3-(2-{[2-(2-pyrrolidin-1-ylethoxy)pyridin-3-yl]oxy}ethoxy)pyrazine;

25 *N,N*-Dimethyl-4-({3-[2-({3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl)oxy]ethoxy}pyridin-2-yl)oxy)butan-1-amine;

N-Methyl-*N*-[2-({3-[2-({3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)ethyl]propan-2-amine;

N,N-Dimethyl-3-({3-[2-({3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)propan-1-amine;

5 *N,N*,2-Trimethyl-1-({3-[2-({3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)propan-2-amine;

[2-({3-[2-({3-[(2*R*)-2-Methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)ethyl]amine;

10 *N*-Methyl-2-({3-[2-({3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)ethanamine;

2-{2-[2-[(2-Dimethylamino)ethoxy]pyridin-3-yl}oxy]ethoxy}-3-[(2*R*)-2,4-dimethylpiperazin-1-yl]pyrazine;

2-[2-(2-[2-(2-Dimethylamino)ethoxy]phenoxy)ethoxy]-3-[(2*R*)-2-methylpiperazin-1-yl]pyrazine;

15 {2-[2-({3-[2-({3-[(2*R*)-2-Methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)ethoxy]ethyl}amine;

[6-({3-[2-({3-[(2*R*)-2-Methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)hexyl]amine;

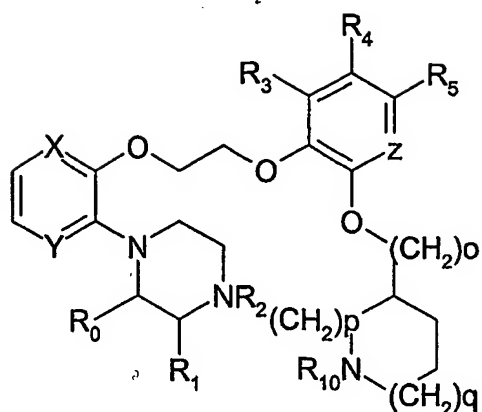
20 [5-({3-[2-({3-[(2*R*)-2-Methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)pentyl]amine

5-({3-[2-({3-[(2*R*)-2,4-Dimethylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)-*N,N*-dimethylpentan-1-amine;

2-[(2*R*)-2-Methylpiperazin-1-yl]-3-(2-([2-(2-piperazin-1-ylethoxy)pyridin-3-yl]oxy)ethoxy)pyrazine.

25

In another preferred embodiment, the invention refers to a compound of Formula (Ib):

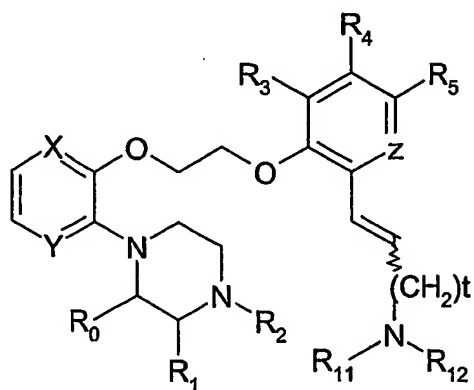


Formula (Ib)

wherein:

- 5 R_0 - R_5 , X, Y, and Z are as defined above,
 o is an integer 0-2;
 p is an integer 0-2, wherein o and p are preferably not both 0;
 q is an integer 0-1;
 R_{10} is H or C₁-C₄-alkyl, preferably H or methyl.
- 10 Specific compounds of Formula (Ib) are:
- 2-[(2*R*)-2-Methylpiperazin-1-yl]-3-[2-({2-[(1-methylpiperidin-4-yl)oxy]pyridin-3-yl}oxy)ethoxy]pyrazine;
 2-[(2*R*)-2-Methylpiperazin-1-yl]-3-[2-({2-[2-(1-methylpyrrolidin-2-yl)ethoxy]pyridin-3-yl}oxy)ethoxy]pyrazine;
 15 2-[(2*R*)-2-Methylpiperazin-1-yl]-3-(2-{[2-(piperidin-3-ylmethoxy)pyridin-3-yl]oxy}ethoxy)pyrazine;
 2-[(2*R*)-2-Methylpiperazin-1-yl]-3-{2-[(2-{{(2*S*)-1-methylpyrrolidin-2-yl}methoxy}pyridin-3-yl)oxy]ethoxy}pyrazine.

- 20 In another preferred embodiment, the invention refers to a compound of Formula (Ic):



Formula (Ic)

wherein:

- 5 R_0 - R_5 , X, Y, and Z are as defined above,
 t is an integer 1-11, preferably 1-8, more preferably 1-6, most preferably 1,
 the orientation around the double bond may be either *cis* or *trans*;

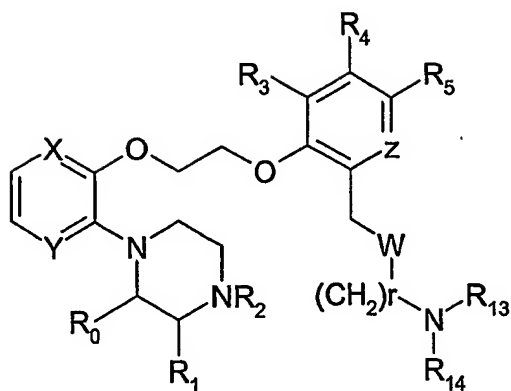
- R_{11} and R_{12} are each independently H or straight or branched C_1 - C_4 -alkyl;
 or R_{11} and R_{12} form together with the nitrogen atom to which they are attached a
 10 saturated heterocyclic ring.

It is preferred that R_{11} and R_{12} are both methyl.

Specific compounds of Formula (Ic) are:

- 2-{2-[{2-[(1Z)-3-(Dimethylamino)prop-1-enyl]pyridin-3-yl}oxy]ethoxy}-3-[(2R)-2-methylpiperazin-1-yl]pyrazine;
 15 2-{2-[{2-[(1E)-3-(Dimethylamino)prop-1-enyl]pyridin-3-yl}oxy]ethoxy}-3-[(2R)-2-methylpiperazin-1-yl]pyrazine.

In another preferred embodiment, the invention refers to a compound of Formula (Id)



Formula (Id)

wherein:

5 R₀-R₅, X, Y, and Z are as defined above,

W is O or CH₂;

r is 1-11, preferably 1-8, more preferably 1-6, most preferably 1 when W is CH₂ and most preferably 2 when W is O;

R₁₃ and R₁₄ are each independently H or straight or branched C₁-C₄-alkyl;

10 or R₁₃ and R₁₄ form together with the nitrogen atom to which they are attached a saturated heterocyclic ring.

In case W is O, then it is preferred that X = N and Y = N. In case W is CH₂, then it is preferred that r = t, X = N, Y = N, R₁₃ = R₁₁ and R₁₄ = R₁₂, where t, R₁₁ and R₁₂ are as defined in formula (Ic).

15 It is preferred that R₁₃ and R₁₄ are both methyl.

Specific compounds of Formula (Id) are:

2-{2-[(2-{[2-(Dimethylamino)ethoxy]methyl}pyridin-3-yl)oxy]ethoxy}-3-[(2R)-2-methylpiperazin-1-yl]pyrazine;

20 2-{2-[(2-{[3-(Dimethylamino)propyl]pyridin-3-yl}oxy]ethoxy}-3-[(2R)-2-methylpiperazin-1-yl]pyrazine.

The compounds of each of Formula (I), (Ia), (Ib), (Ic) and (Id) are collectively referred to as those of Formulae (I).

In case the compounds of Formulae (I) contain groups which may exist in tautomeric forms, the invention comprises the tautomeric forms of the compounds as well as mixtures thereof.

25

In case the compounds of Formulae (I) can be in the form of geometrical isomers, the invention comprises the geometrical isomers as well as mixtures thereof.

In another aspect, the invention provides the compounds according to Formulae (I) above for use in therapy of a human being or an animal.

5 Still another aspect of the invention provides a pharmaceutical composition comprising a compound according to Formulae (I) above as the active ingredient, preferably together with a pharmaceutically acceptable carrier and, if desired, other pharmacologically active agents.

10 In yet another aspect, the invention provides a method for the treatment of a human or animal subject suffering from a serotonin-related disorder or condition, particularly 5-HT_{2C} receptor-related, such as memory disorders, such as Alzheimer's disease; schizophrenia; mood disorders such as depression; anxiety disorders; pain; substance abuse; sexual dysfunctions such as erectile dysfunction; epilepsy; glaucoma; urinary disorders, such as urinary incontinence; menopausal and post-menopausal hot flushes; type 2 diabetes; eating
15 disorders, such as binge eating disorders, anorexia nervosa and bulimia; weight gain associated with antipsychotic drug administration, premenstrual tension, sleep disorders; and particularly obesity.

Another aspect of the invention provides the use of the compounds according to Formulae (I) above for the manufacture of a medicament for the treatment of a serotonin-
20 related disorder or condition, particularly 5-HT_{2C} receptor-related, such as memory disorders, such as Alzheimer's disease; schizophrenia; mood disorders such as depression; anxiety disorders; pain; substance abuse; sexual dysfunctions such as erectile dysfunction; epilepsy; glaucoma; urinary disorders, such as urinary incontinence; menopausal and post-menopausal hot flushes; type 2 diabetes; eating disorders, such as binge eating disorders,
25 anorexia nervosa and bulimia; weight gain associated with antipsychotic drug administration, premenstrual tension, sleep disorders; and particularly obesity. The method can include administering to a subject (e.g., a human or an animal) in need thereof an effective amount of one or more compounds of Formulae (I), their salts, or compositions containing the compounds or salts.

30 Another aspect of the invention provides methods for modulating 5-HT_{2C} receptor function comprising contacting the receptor with an effective stimulatory or inhibitory amount of a compound according to Formulae (I) above, preferably an effective stimulatory amount thereof.

The methods delineated herein can also include the step of identifying that the subject is in need of treatment of the serotonin-related disorder or condition. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g., opinion) or objective (e.g., measurable by a test or diagnostic method).

5 This invention also features a method for preparing a composition. The method includes combining a compound of Formulae (I) with a pharmaceutically acceptable carrier.

Still another aspect of the invention provides methods for the preparation of the compounds according to Formulae (I) above.

A further aspect of the invention relates to a method for treating a disorder or
10 condition, comprising administering to a subject in need thereof an effective amount of a compound of Formulae (I) above, wherein the disorder or condition is selected from memory disorders including Alzheimer's disease; schizophrenia; mood disorders such as depression; anxiety disorders; pain; substance abuse; sexual dysfunctions such as erectile dysfunction; epilepsy; glaucoma; urinary disorders, such as urinary incontinence; menopausal and post-
15 menopausal hot flushes; type 2 diabetes; eating disorders, such as binge eating disorders, anorexia nervosa and bulimia; weight gain associated with antipsychotic drug administration, premenstrual tension, sleep disorders; and particularly obesity.

A still further aspect of the invention relates to the use of the compounds of Formulae (I) above for the manufacture of a medicament for the treatment of memory disorders
20 including Alzheimer's disease; schizophrenia; mood disorders such as depression; anxiety disorders; pain; substance abuse; sexual dysfunctions such as erectile dysfunction; epilepsy; glaucoma; urinary disorders, such as urinary incontinence; menopausal and post-menopausal hot flushes; type 2 diabetes; eating disorders, such as binge eating disorders, anorexia nervosa and bulimia; weight gain associated with antipsychotic drug administration, premenstrual
25 tension, sleep disorders; and particularly obesity.

Detailed description of the invention

First, the various terms used, separately and in combinations, in the above definition of the compounds having the general Formula (I) (and each of Formulae (I)) will be explained.

30 C₁-C₄-alkyl, which may be straight or branched, is an alkyl group having 1-4 carbon atoms. Exemplary alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl.

Amino-C₂-C₄-alkyl, which may be straight or branched, is a C₂-C₄-alkyl group directly attached to an amino group. Exemplary aminoalkyl groups include 2-aminoethyl, 3-amino-n-propyl, and 4-amino-n-butyl.

5 C₃-C₆-cycloalkyl is a cyclic alkyl group having 3-6 carbon atoms. Exemplary cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

C₁-C₄-acyl, which may be straight or branched, is an acyl group having 1-4 carbon atoms. Exemplary acyl groups include formyl, acetyl, propionyl, n-butyryl, and isobutyryl.

C₁-C₄-alkoxy, which may be straight or branched, is an alkoxy group having 1-4 carbon atoms. Exemplary alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-
10 butoxy, sec-butoxy, isobutoxy, and tert-butoxy.

C₁-C₄-alkoxycarbonyl means a C₁-C₄-alkoxy group directly connected to a carbonyl group. An exemplary alkoxycarbonyl group is tert-butoxycarbonyl (*t*-BOC).

DCM means dichloromethane, DMSO means dimethylsulfoxide, halogen means fluoro, chloro, bromo, or iodo, HOAc means acetic acid, HPLC means high performance
15 liquid chromatography, HRMS means high resolution mass spectrometry, "OTs" means tosylate i.e. para-toluenesulfonate, "OMs" means mesylate i.e. methanesulfonate, TEA means triethylamine, TFA means trifluoroacetic acid, THF means tetrahydrofuran.

The term "saturated heterocyclic" refers to a heterocyclic ring that is non-aromatic (e.g., partially or fully saturated) and that has carbon atoms and one or two heteroatoms
20 selected from O, S, and N (preferably from O and N and more preferably from N). Examples of saturated heterocyclic rings have 4-7 members and include piperidine, azetidine, morpholine, thiomorpholine, pyrrolidine, and piperazine.

Hydrogenation catalyst means a catalyst suitable for catalytic hydrogenation or debenzoylation. Examples of hydrogenation catalysts are palladium on carbon (Pd/C),
25 Raney-Nickel, platinum, platinum oxide and zinc oxide.

Hydrogen source means a reagent used to introduce a hydrogen atom on any atom of a compound, including a carbon or oxygen atom. Examples of hydrogen sources are hydrogen gas and ammonium formate.

Hydroxyethylating agent means a reagent used to introduce a hydroxyethyl group on
30 an oxygen or nitrogen atom of a compound. Examples of hydroxyethylating agents are ethylene carbonate, 2-bromoethanol, 2-chloroethanol and ethylene oxide.

For the transformation of an alcohol function into an aldehyde function, the method by Swern et al., J. Org. Chem. 1978, 43, 2480-2482, may be used. According to this method, the

alcohol is reacted with dimethyl sulfoxide and oxalyl chloride in dichloromethane at a temperature of -78°C .

For the transformation of an alcohol function into a suitable leaving group, one may treat the alcohol with methanesulfonic anhydride in the presence of triethylamine in dichloromethane at a temperature of 0°C , e.g. as disclosed in J. Org. Chem. 2000, 65, 7839-7846.

A base is any substance that produces a negative ion and donates electrons to an acid, if present. The term "base" as used herein, represents a reagent capable of accepting protons during the course of a reaction. Examples of bases include carbonate salts such as potassium carbonate, potassium bicarbonate, sodium carbonate, sodium bicarbonate, and cesium carbonate; halides such as cesium fluoride; phosphates such as potassium phosphate, potassium dihydrogen phosphate, and potassium hydrogen phosphate; hydroxides such as lithium hydroxide, sodium hydroxide, and potassium hydroxide; alkoxides such as sodium tert-butoxide, potassium tert-butoxide, and lithium tert-butoxide; alkylamines such as triethylamine, diisopropylamine, and diisopropylethylamine; heterocyclic amines such as 4-dimethylaminopyridine, 2,6-lutidine, 1-methylimidazole, pyridine; bicyclic amines such as 1,8-diazabicyclo(4.3.0)undec-7-ene; and hydrides such as lithium hydride, sodium hydride, and potassium hydride. The base chosen for a particular conversion depends on the nature of the starting materials, the solvent or solvents in which the reaction is conducted, and the temperature at which the reaction is conducted.

The term "prodrug forms" means a pharmacologically acceptable derivative, such as an ester or an amide, which derivative is biotransformed in the body to form the active drug. Reference is made to Goodman and Gilman's, The Pharmacological basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs, p. 13-15; and "The Organic Chemistry of Drug Design and Drug Action" by Richard B. Silverman. Chapter 8, p 352. (Academic Press, Inc. 1992. ISBN 0-12-643730-0).

"Pharmaceutically acceptable" means being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" mean salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with organic and inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, glycolic acid, maleic acid, malonic acid, malic acid, oxalic acid, toluenesulphonic acid, methanesulphonic

acid, trifluoroacetic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, ascorbic acid, isethionic acid (i.e. 2-hydroxyethylsulphonic acid) and the like.

"Treatment" as used herein includes prophylaxis of the named disorder or condition, or amelioration or elimination of the disorder or condition once it has been established.

5 It should be noted that both E- and Z-isomers of the compounds, optical isomers, as well as mixtures thereof, and all isotopes are included within the scope of the invention. E means "entgegen" (trans-isomer) and Z means "zusammen" (cis-isomer).

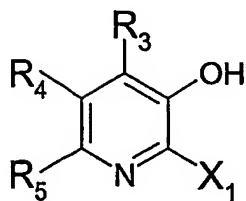
Presently preferred compounds of the general Formula (I) above are the compounds according to Examples 1-3 and 6-27; and their pharmacologically
10 acceptable salts and solvates.

As mentioned above, the compounds of the present invention are useful for the treatment of a human or animal subject suffering from a serotonin-related disorder or condition, particularly 5-HT_{2C} receptor-related, such as memory disorders, such as Alzheimer's disease; schizophrenia; mood disorders such as depression; anxiety disorders;
15 pain; substance abuse; sexual dysfunctions such as erectile dysfunction; epilepsy; glaucoma; urinary disorders, such as urinary incontinence; menopausal and post-menopausal hot flushes; type 2 diabetes; eating disorders, such as binge eating disorders, anorexia nervosa and bulimia; weight gain associated with antipsychotic drug administration, premenstrual tension, sleep disorders; and particularly obesity. The 5-HT_{2C} receptor-related disorder includes any
20 disorder or condition that is modulated by the 5-HT_{2C} receptor. Preferably, the compounds of the present invention may be used in the treatment of disorders and conditions where a 5-HT_{2C} receptor agonist is desired or required.

The compounds of the present invention in labelled form, e.g. isotopically labelled, may be used as a diagnostic agent. Examples of such labels are known in the art and include
25 ¹³¹I, ³⁵S, ³²P, ¹⁸F, ¹⁴C, ¹¹C, ³H, and the like.

Another object of the present invention is a process for the preparation of a compound of the Formula (Ia), which process comprises:

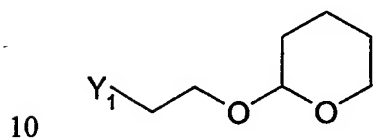
a) reacting a compound of Formula (II)



Formula (II)

wherein:

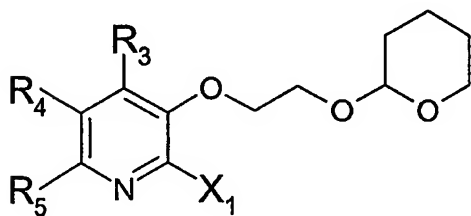
- 5 X_1 is selected from F, Cl, Br and I,
 R_3 - R_5 are each independently H, halogen, methyl or methoxy, provided that at least one of R_3 - R_5 is hydrogen,
 with a compound of Formula (III):



Formula (III)

wherein Y_1 is a suitable leaving group selected from Cl, Br, I, OTs, or OMs;

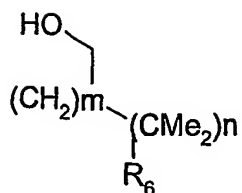
- 15 in the presence of a base, such as potassium carbonate, triethylamine, or pyridine, in a solvent such as acetonitrile, to give a compound of Formula (IV):



Formula (IV)

- 20 wherein X_1 and R_3 - R_5 are as defined above;

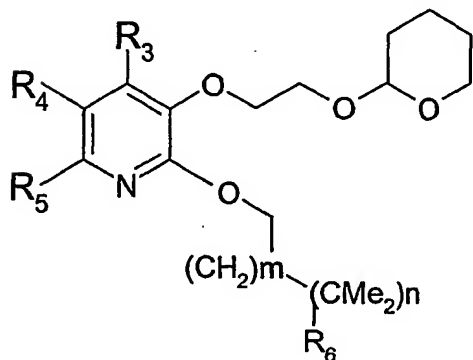
b) reacting the compound of Formula (IV) with a compound of Formula (Va) in the presence of a base, such as potassium tert-butoxide, in a solvent, such as toluene,



Formula (Va)

wherein:

- 5 m is an integer 0-10, preferably 0-7, more preferably 0-5,
 n is an integer 0 or 1, wherein the sum of m+n is preferably at least 1,
 R₆ is NR₇R₈ or OR₉, wherein
 R₇ and R₈ are each independently H or straight or branched C₁-C₄-alkyl;
 or R₇ and R₈ form together with the nitrogen atom to which they are attached a saturated
 10 heterocyclic ring;
 R₉ is amino-C₂-C₄-alkyl or N,N-di-C₁-C₄-alkylamino-C₂-C₄-alkyl,
 to give a compound of Formula (VIa):



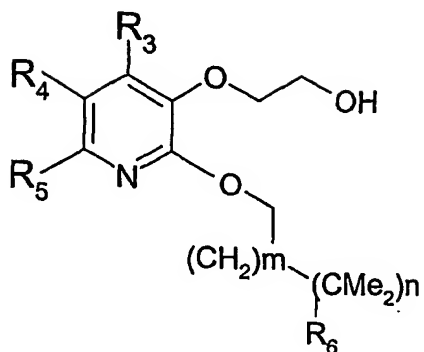
15

Formula (VIa)

wherein:

R₃-R₆, m, and n are as defined above,

- 20 c) treating the compound of Formula (VIa) with an aqueous acid such as aqueous acetic acid
 or aqueous hydrochloric acid, to give a compound of Formula (VIIa):



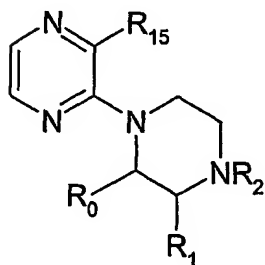
Formula (VIIa)

wherein:

- 5 R₃-R₆, m, and n are as defined above,

d) reacting the compound of Formula (VIIa) with a compound of Formula (VIII) in the presence of a base, such as potassium tert-butoxide, in a solvent, such as methyl tert-butyl ether or toluene,

10

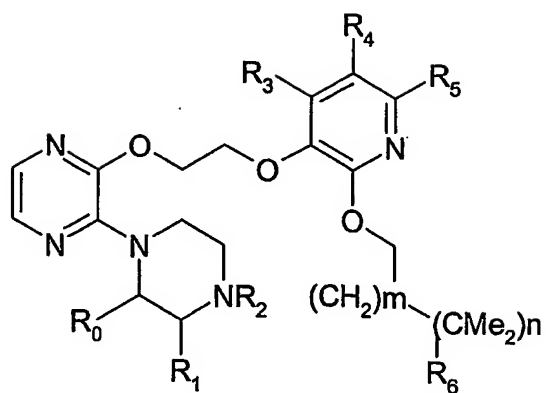


Formula (VIII)

wherein

- 15 R₀ and R₁ are each independently H or CH₃;
 R₂ is selected from C₁-C₄-alkoxycarbonyl, benzyl, trityl, C₁-C₄-alkyl, 2-hydroxyethyl, 2-cyanoethyl, tetrahydropyran-2-yl, and C₁-C₄-acyl,
 R₁₅ is halogen, such as chlorine, to give a compound of Formula (Ia) wherein X = N and Y = N:

20



Formula (Ia)

wherein R_0 - R_6 , m , and n are as defined above;

5

e) if desired, separating a racemate obtained into optical isomers and/or forming an acid addition salt with an organic or inorganic acid,

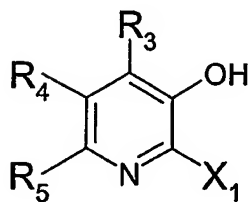
f) if R_2 in Formula (Ia) following step d) is a nitrogen protecting group, such as *t*-BOC, trityl, and benzyl, removing said nitrogen protecting group, such as under acidic conditions (e.g. trifluoroacetic acid in a solvent such as chloroform), hydrogenolytic or non-hydrogenolytic conditions, to provide the compound of Formula (Ia), wherein R_2 is hydrogen.

10

Another object of the present invention is a process for the preparation of a compound of the Formula (Ib), which process comprises:

15

a) reacting a compound of Formula (II)



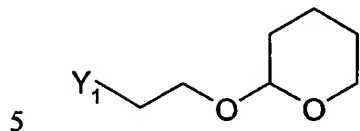
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Formula (II)

wherein:

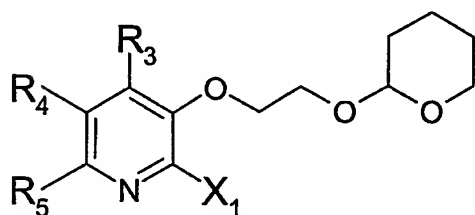
X_1 is selected from F, Cl, Br and I,

R_3 - R_5 are each independently H, halogen, methyl or methoxy, provided that at least one of R_3 - R_5 is hydrogen,
with a compound of Formula (III):



Formula (III)

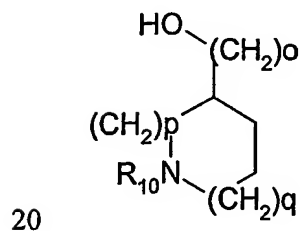
wherein Y_1 is a suitable leaving group selected from Cl, Br, I, OTs, or OMs;
in the presence of a base, such as potassium carbonate, triethylamine, or pyridine, in a solvent,
10 such as acetonitrile, to give a compound of Formula (IV):



Formula (IV)

15 wherein X_1 and R_3 - R_5 are as defined above;

b) reacting the compound of Formula (IV) with a compound of Formula (Vb) in the presence
of a base, such as potassium tert-butoxide, in a solvent, such as toluene,



Formula (Vb)

wherein:

o is an integer 0-2;

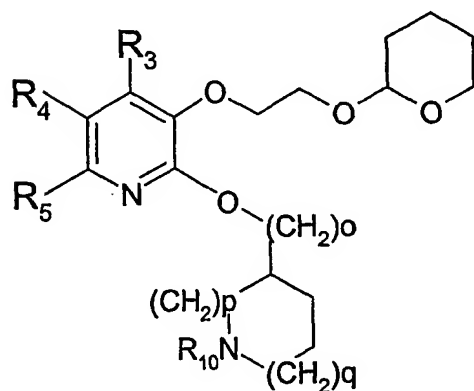
p is an integer 0-2, wherein o and p are preferably not both 0;

q is an integer 0-1;

R₁₀ is H or C₁-C₄-alkyl, preferably H or methyl;

to give a compound of Formula (VIb):

5

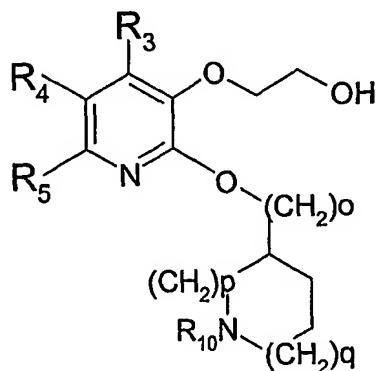


Formula (VIb)

wherein:

10 R₃-R₅ and R₁₀, o, p, and q are as defined above,

c) treating the compound of Formula (VIb) with an aqueous acid such as aqueous acetic acid or aqueous hydrochloric acid, to give a compound of Formula (VIIb):



15

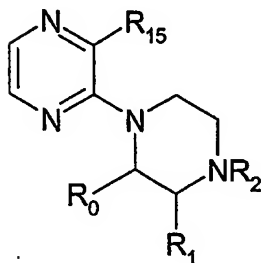
Formula (VIIb)

wherein:

R₃-R₅ and R₁₀, o, p, and q are as defined above,

20

d) reacting the compound of Formula (VIIb) with a compound of Formula (VIII) in the presence of a base such as potassium tert-butoxide, in a solvent, such as methyl tert-butyl ether or toluene,



5

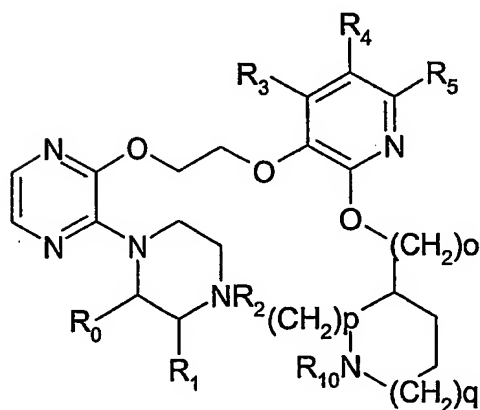
Formula (VIII)

wherein

R_0 and R_1 are each independently H or CH_3 ;

- 10 R_2 is selected from C_1 - C_4 -alkoxycarbonyl, benzyl, trityl, C_1 - C_4 -alkyl, 2-hydroxyethyl, 2-cyanoethyl, tetrahydropyran-2-yl, and C_1 - C_4 -acyl,

R_{15} is halogen, such as chlorine, to give a compound of Formula (Ib) wherein $X = N$ and $Y = N$:



15

Formula (Ib)

wherein R_0 - R_5 , R_{10} , o , p , and q are as defined above;

- 20 e) if desired, separating a racemate obtained into optical isomers and/or forming an acid addition salt with an organic or inorganic acid,

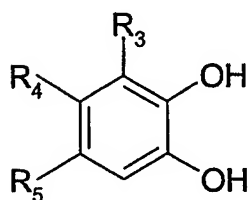
f) if R_2 in Formula (Ib) following step d) is a nitrogen protecting group, such as *t*-BOC, trityl, and benzyl, removing said nitrogen protecting group, such as under acidic conditions (e.g. trifluoroacetic acid in a solvent such as chloroform), hydrogenolytic or non-hydrogenolytic conditions, to provide the compound of Formula (Ib), wherein R_2 is hydrogen.

5

Another object of the present invention is a process for the preparation of a compound of the Formula (Ia), which process comprises:

- a) reacting a compound of Formula (IX) with a benzylating agent, such as benzyl chloride, benzyl bromide, or benzyl tosylate, in the presence of a base:

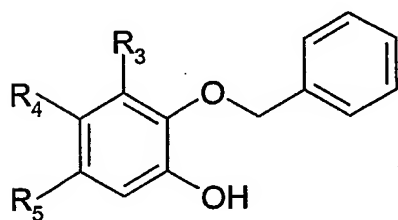
10



Formula (IX)

- wherein R_3 - R_5 are each independently H, halogen, methyl, and methoxy, provided that at least one of R_3 - R_5 is hydrogen, to give a compound of Formula (X):

15



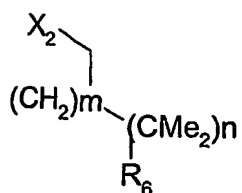
Formula (X)

20

wherein R_3 - R_5 are as defined above,

- b) reacting the compound of Formula (X) with a compound of Formula (XIa) in the presence of a base, such as potassium carbonate, in a solvent, such as acetone:

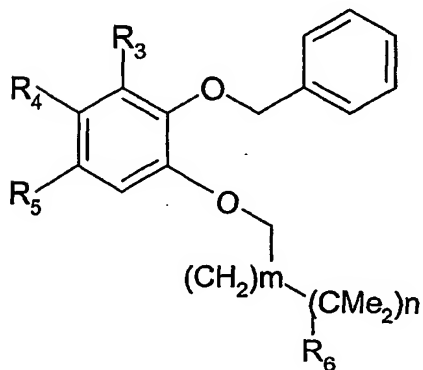
25



Formula (XIa)

wherein

- 5 X_2 is halogen, OMs, or OTs;
 m is an integer 0-10, preferably 0-7, more preferably 0-5,
 n is an integer 0 or 1, wherein the sum of $m+n$ is preferably at least 1,
 R_6 is NR_7R_8 or OR_9 , wherein
 R_7 and R_8 are each independently H or straight or branched C_1 - C_4 -alkyl;
10 or R_7 and R_8 form together with the nitrogen atom to which they are attached a saturated heterocyclic ring;
 R_9 is amino- C_2 - C_4 -alkyl or N,N-di- C_1 - C_4 -alkylamino- C_2 - C_4 -alkyl,
to give a compound of Formula (XIIa):

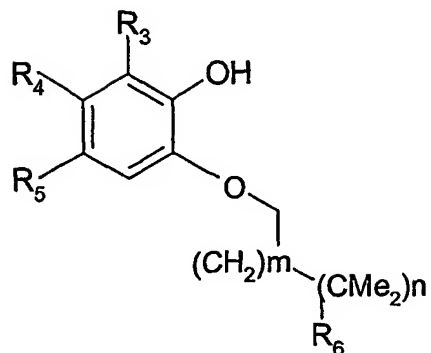


Formula (XIIa)

wherein

R_3 - R_6 , m , and n are as defined above;

c) treating the compound of Formula (XIIa) with hydrogen in the presence of a hydrogenation catalyst, such as palladium on carbon, in a solvent, such as methanol, to give a compound of Formula (XIIIa):

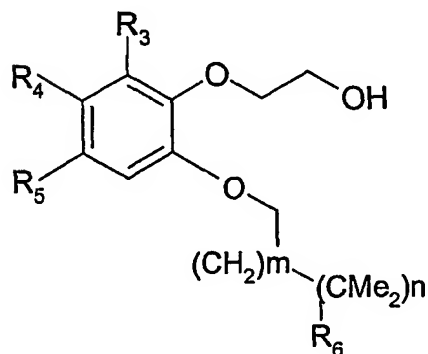


Formula (XIIIa)

wherein R_3 - R_6 , m , and n are as defined above;

5

d) reacting the compound of Formula (XIIIa) with a hydroxyethylating agent such as ethylene carbonate in the presence of a base, such as potassium carbonate, in a solvent, such as N,N-dimethylformamide, to give a compound of Formula (XIVa):



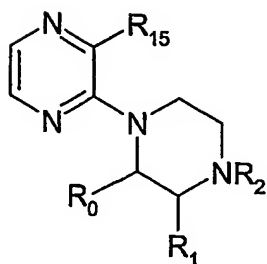
10

Formula (XIVa)

wherein R_3 - R_6 , m , and n are as defined above;

15

e) reacting the compound of Formula (XIVa) with a compound of Formula (VIII) in the presence of a base such as potassium tert-butoxide, in a solvent, such as N,N-dimethylformamide:

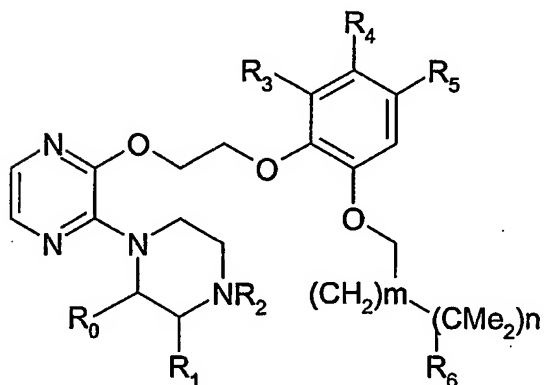


Formula (VIII)

wherein

- 5 R₀ and R₁ are each independently H or CH₃;
 R₂ is selected from C₁-C₄-alkoxycarbonyl, benzyl, trityl, C₁-C₄-alkyl, 2-hydroxyethyl, 2-cyanoethyl, tetrahydropyran-2-yl, and C₁-C₄-acyl,
 R₁₅ is halogen, such as chlorine, to give a compound of Formula (Ia) wherein X = N and Y = N:

10



Formula (Ia)

wherein R₀-R₆, m, and n are as defined above;

15

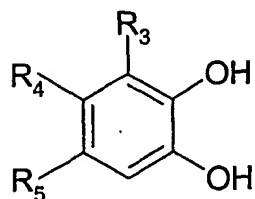
f) if desired, separating a racemate obtained into optical isomers and/or forming an acid addition salt with an organic or inorganic acid,

20

g) if R₂ in Formula (Ia) following step e) is a nitrogen protecting group, such as *t*-BOC, trityl, and benzyl, removing said nitrogen protecting group, such as under acidic conditions (e.g. trifluoroacetic acid in a solvent such as chloroform), hydrogenolytic or non-hydrogenolytic conditions, to provide the compound of Formula (Ia), wherein R₂ is hydrogen.

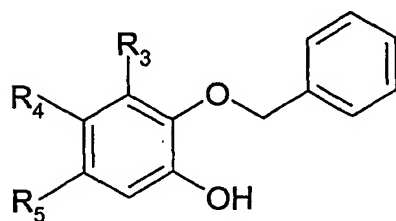
Another object of the present invention is a process for the preparation of a compound of the Formula (Ib), which process comprises:

- 5 a) reacting a compound of Formula (IX) with a benzylating agent, such as benzyl chloride, benzyl bromide, or benzyl tosylate, in the presence of a base:



- 10 Formula (IX)

wherein R_3 - R_5 are each independently H, halogen, methyl, or methoxy, provided that at least one of R_3 - R_5 is hydrogen, to give a compound of Formula (X):

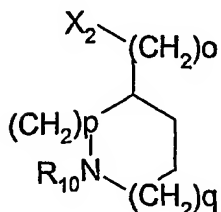


15

Formula (X)

wherein R_3 - R_5 are as defined above,

- b) reacting the compound of Formula (X) with a compound of Formula (XIb) in the presence
20 of a base, such as potassium carbonate, in a solvent, such as acetone:



Formula (XIb)

wherein:

X_2 is halogen, OMs, or OTs;

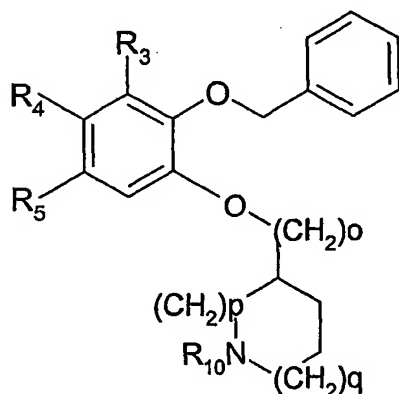
o is an integer 0-2;

5 p is an integer 0-2, wherein o and p are preferably not both 0;

q is an integer 0-1;

R_{10} is H or C_1 - C_4 -alkyl, preferably H or methyl;

to give a compound of Formula (XIb):



10

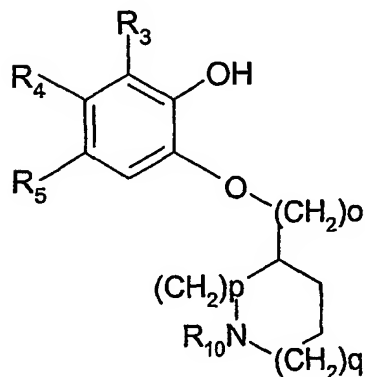
Formula (XIIb):

wherein:

R_3 - R_5 , R_{10} , o , p , and q are as defined above,

15

c) treating the compound of Formula (XIIb) with hydrogen in the presence of a hydrogenation catalyst, such as palladium on carbon, in a solvent, such as methanol, to give a compound of Formula (XIIIb):



20

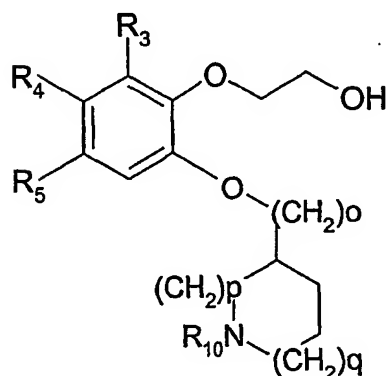
Formula (XIIIb):

wherein:

R₃-R₅, R₁₀, o, p, and q are as defined above,

5

d) reacting the compound of Formula (XIIIb) with a hydroxyethylating agent such as ethylene carbonate in the presence of a base, such as potassium carbonate, in a solvent, such as N,N-dimethylformamide, to give a compound of Formula (XIVb):



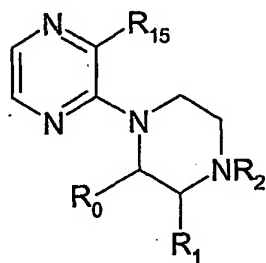
10

Formula (XIVb)

wherein R₃-R₅, R₁₀, o, p, and q are as defined above;

15

e) reacting the compound of Formula (XIVa) with a compound of Formula (VIII) in the presence of a base, such as potassium tert-butoxide, in a solvent, such as N,N-dimethylformamide,



20

Formula (VIII)

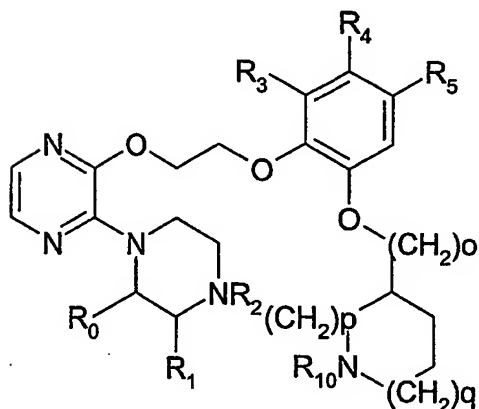
wherein

R_0 and R_1 are each independently H or CH_3 ;

R_2 is selected from C_1 - C_4 -alkoxycarbonyl, benzyl, trityl, C_1 - C_4 -alkyl, 2-hydroxyethyl, 2-cyanoethyl, tetrahydropyran-2-yl, and C_1 - C_4 -acyl,

R_{15} is halogen, such as chlorine, to give a compound of Formula (Ib) wherein $X = \text{N}$ and $Y =$

5 N:



Formula (Ib)

wherein R_0 - R_5 , R_{10} , o , p , and q are as defined above;

10

f) if desired, separating a racemate obtained into optical isomers and/or forming an acid addition salt with an organic or inorganic acid,

g) if R_2 in Formula (Ib) following step e) is a nitrogen protecting group, such as *t*-BOC, trityl, and benzyl, removing said nitrogen protecting group, such as under acidic conditions (e.g., trifluoroacetic acid in a solvent such as chloroform), hydrogenolytic or non-hydrogenolytic conditions, to provide the compound of Formula (Ib), wherein R_2 is hydrogen.

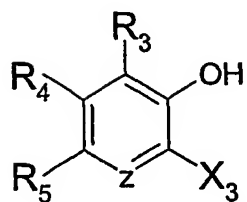
15

Another object of the present invention is a process for the preparation of a compound of the Formula (Ia), which process comprises:

20

a) reacting a compound of Formula (XV) with a compound selected from benzyl chloride, benzyl bromide, benzyl iodide, benzyl tosylate, and benzyl mesylate in the presence of a base, such as potassium carbonate, in a solvent, such as *N,N*-dimethylformamide,

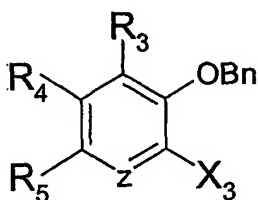
25



Formula (XV)

wherein:

- 5 X_3 is selected from Cl, Br and I, Z is CH or N,
 R_3 - R_5 are each independently H, halogen, methyl or methoxy, provided that at least one of R_3 - R_5 is hydrogen, to give a compound of Formula (XVI):

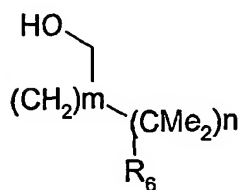


10

Formula (XVI)

wherein R_3 - R_5 , X_3 , and Z are as defined above;

- b) reacting the compound of Formula (XVI) with a compound of Formula (Va) in the
 15 presence of a base, such as sodium tert-butoxide, in a solvent, such as N,N-dimethylformamide,



20 Formula (Va)

wherein:

m is an integer 0-10, preferably 0-7, more preferably 0-5,

n is an integer 0 or 1, wherein the sum of m+n is preferably at least 1,

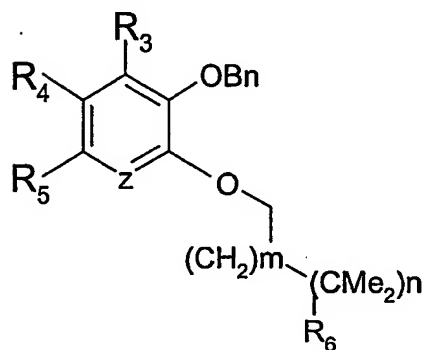
R_6 is NR_7R_8 or OR_9 , wherein

R₇ and R₈ are each independently H or straight or branched C₁-C₄-alkyl;

or R₇ and R₈ form together with the nitrogen atom to which they are attached a saturated heterocyclic ring;

R₉ is amino-C₂-C₄-alkyl or N,N-di-C₁-C₄-alkylamino-C₂-C₄-alkyl,

5 to give a compound of Formula (XVIIa):



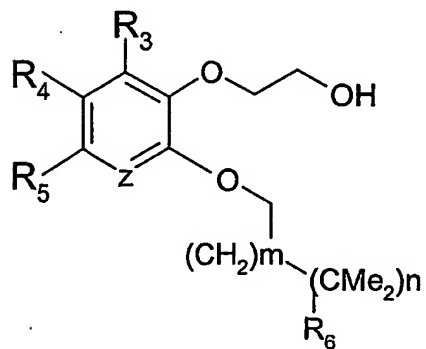
Formula (XVIIa)

10 wherein:

R₃-R₆, m, n, and Z are as defined above,

c) treating the compound of Formula (XVIIa) with a hydrogenation catalyst using a suitable hydrogen source such as ammonium formate and then heating in the presence of a

15 hydroxyethylating agent, preferably ethylene carbonate, and a base, such as potassium carbonate, in a solvent, such as N,N-dimethylformamide, to give a compound of Formula (VIIa):



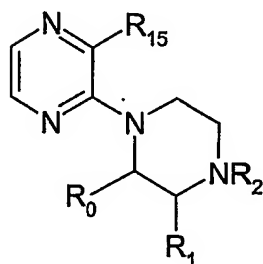
20

Formula (VIIa)

wherein:

R_3 - R_6 , m , n , and Z are as defined above,

- d) reacting the compound of Formula (VIIa) with a compound of Formula (VIII) in the presence of a base, such as sodium *tert*-butoxide, in a solvent, such as *N,N*-dimethylformamide,



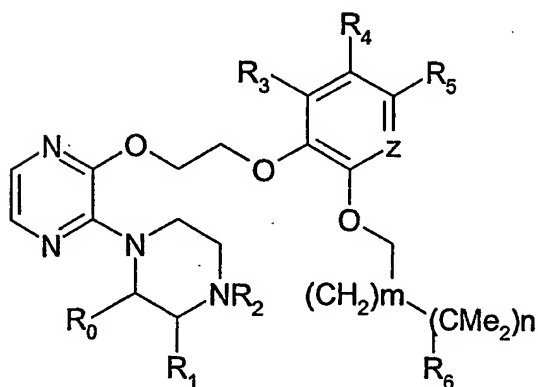
10 Formula (VIII)

wherein

R_0 and R_1 are each independently H or CH_3 ;

R_2 is selected from C_1 - C_4 -alkoxycarbonyl, benzyl, trityl, C_1 - C_4 -alkyl, 2-hydroxyethyl, 2-cyanoethyl, tetrahydropyran-2-yl, and C_1 - C_4 -acyl,

- 15 R_{15} is halogen, such as chlorine, to give a compound of Formula (Ia) wherein $X = N$ and $Y = N$:



20 Formula (Ia)

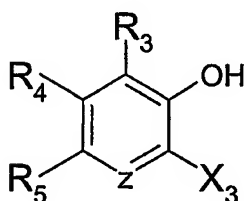
wherein R_0 - R_6 , m , n , and Z are as defined above;

e) if desired, separating a racemate obtained into optical isomers and/or forming an acid addition salt with an organic or inorganic acid,

f) if R_2 in Formula (Ia) following step d) is a nitrogen protecting group, such as *t*-BOC, trityl, and benzyl, removing said nitrogen protecting group, such as under acidic conditions (e.g. trifluoroacetic acid in a solvent such as chloroform), hydrogenolytic or non-hydrogenolytic conditions, to provide the compound of Formula (Ia), wherein R_2 is hydrogen.

Another object of the present invention is a process for the preparation of a compound of the Formula (Ib), which process comprises:

a) reacting a compound of Formula (XV) with a compound selected from benzyl chloride, benzyl bromide, benzyl iodide, benzyl tosylate, and benzyl mesylate in the presence of a base, such as potassium carbonate, in a solvent, such as N,N-dimethylformamide,

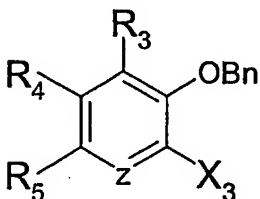


Formula (XV)

wherein:

X_1 is selected from Cl, Br and I, Z is CH or N,

R_3 - R_5 are each independently H, halogen, methyl or methoxy, provided that at least one of R_3 - R_5 is hydrogen, to give a compound of Formula (XVI):

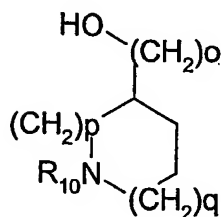


Formula (XVI)

wherein R_3 - R_5 , X_3 , and Z are as defined above;

b) reacting the compound of Formula (XVI) with a compound of Formula (Vb) in the presence of a base, such as sodium tert-butoxide, in a solvent, such as N,N-dimethylformamide,

5



Formula (Vb)

wherein:

10 o is an integer 0-2;

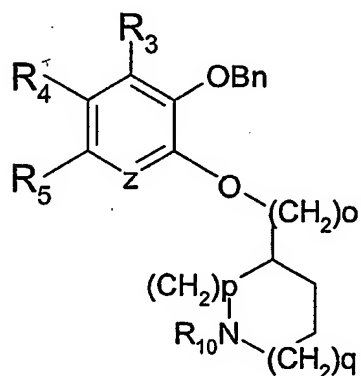
p is an integer 0-2, wherein o and p are preferably not both 0;

q is an integer 0-1;

R₁₀ is H or C₁-C₄-alkyl, preferably H or methyl;

to give a compound of Formula (XVIIb):

15



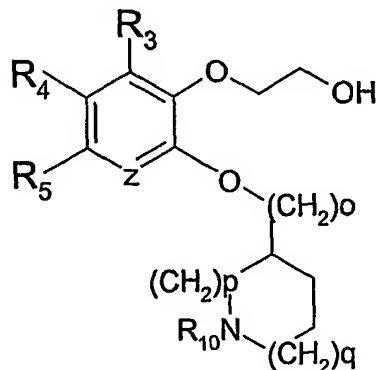
Formula (XVIIb)

wherein:

20 R₃-R₅ and R₁₀, o, p, q, and Z are as defined above,

c) treating the compound of Formula (XVIIb) with a hydrogenation catalyst using a suitable hydrogen source such as ammonium formate and then heating in the presence of a

hydroxyethylating agent, preferably ethylene carbonate, and a base, such as potassium carbonate, in a solvent, such as N,N-dimethylformamide, to give a compound of Formula (VIIb):



5

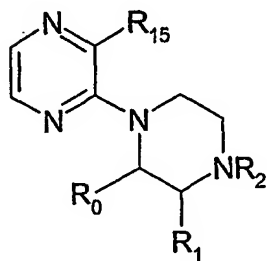
Formula (VIIb)

wherein:

R₃-R₅ and R₁₀, o, p, q, and Z are as defined above,

10

d) reacting the compound of Formula (VIIb) with a compound of Formula (VIII) in the presence of a base such as sodium tert-butoxide, in a solvent, such as N,N-dimethylformamide,



15

Formula (VIII)

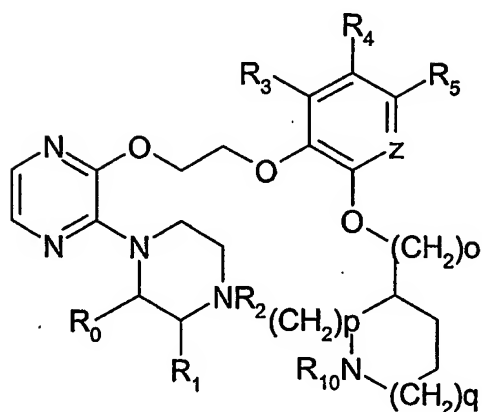
wherein

R₀ and R₁ are each independently H or CH₃;

R₂ is selected from C₁-C₄-alkoxycarbonyl, benzyl, trityl, C₁-C₄-alkyl, 2-hydroxyethyl, 2-cyanoethyl, tetrahydropyran-2-yl, and C₁-C₄-acyl,

20

R₁₅ is halogen, such as chlorine, to give a compound of Formula (Ib) wherein X = N and Y = N:



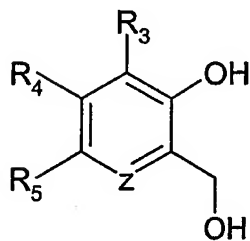
5

Formula (Ib)

wherein R₀-R₅, R₁₀, o, p, q, and Z are as defined above;

- e) if desired, separating a racemate obtained into optical isomers and/or forming an acid addition salt with an organic or inorganic acid,
- f) if R₂ in Formula (Ib) following step d) is a nitrogen protecting group, such as *t*-BOC, trityl, and benzyl, removing said nitrogen protecting group, such as under acidic conditions (e.g. trifluoroacetic acid in a solvent such as chloroform), hydrogenolytic or non-hydrogenolytic conditions, to provide the compound of Formula (Ib), wherein R₂ is hydrogen.

- a) reacting a compound of formula (XVIII):



Formula (XVIII)

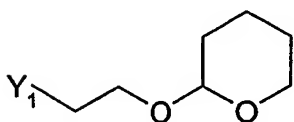
wherein:

R₃-R₅ are each independently H, halogen, methyl or methoxy, provided that at least one of R₃-

5 R₅ is hydrogen;

Z is CH or N,

with a compound of Formula (III):



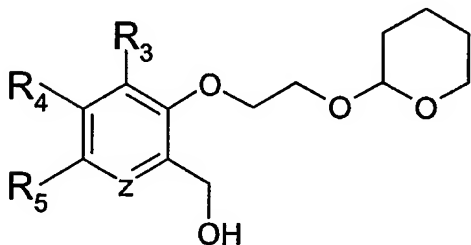
10

Formula (III)

wherein Y₁ is a suitable leaving group selected from Cl, Br, I, OTs, or OMs;

in the presence of a base, such as potassium carbonate, triethylamine, or pyridine, in a solvent, such as acetonitrile, to give a compound of Formula (XIX):

15

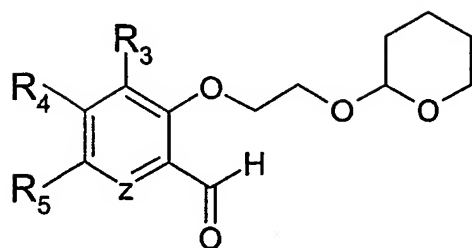


Formula (XIX)

wherein R₃-R₅ and Z are as defined above,

20

b) transforming the alcohol function in the compound of Formula (XVI) into an aldehyde function with dimethyl sulfoxide and oxalyl chloride in dichloromethane, to give a compound of Formula (XX):



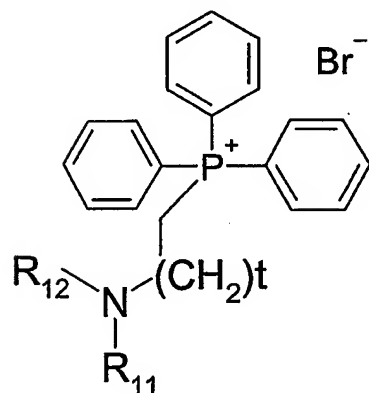
Formula (XX)

5 wherein:

R₃-R₅ and Z are as defined above,

c) reacting the compound of Formula (XX) with a compound of Formula (XXI) in the presence of a base, such as potassium tert-butoxide in a solvent mixture consisting of

10 tetrahydrofuran and tert-butanol,



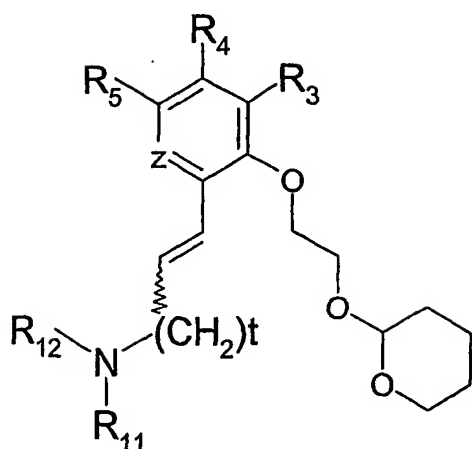
Formula (XXI)

15 wherein:

t is an integer 1-11, preferably 1-8, more preferably 1-6, most preferably 1; and

R₁₁ and R₁₂ are each independently H or straight or branched C₁-C₄-alkyl; or R₁₁ and R₁₂ form together with the nitrogen atom to which they are attached a saturated heterocyclic ring, to give a compound of Formula (XXII):

20



Formula (XXII)

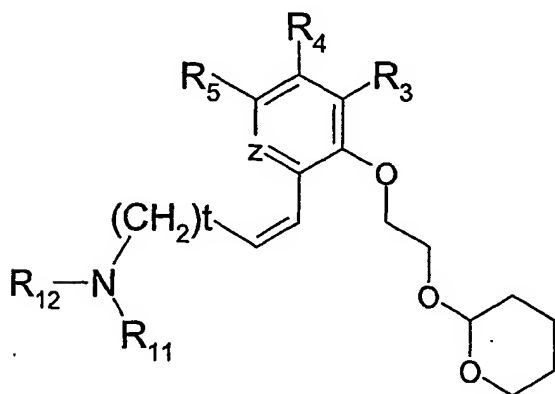
wherein:

- 5 R_3 - R_5 , R_{11} , R_{12} , t , and Z are as defined above;

the orientation around the double bond may be either *cis* or *trans*;

d) separation by preparative HPLC and isolation of the *cis* and *trans* isomers of compound of Formula (XXII) to provide the individual *cis* isomer of Formula (XXIII) and the individual

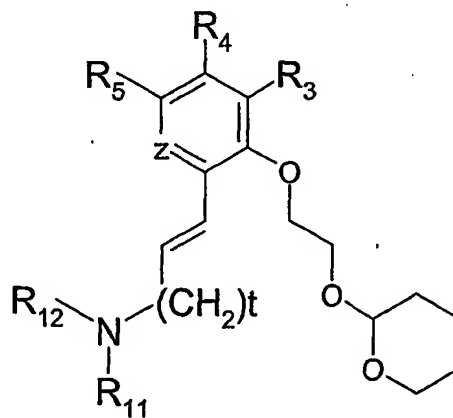
- 10 *trans* isomer of Formula (XXIV)



Formula (XXIII)

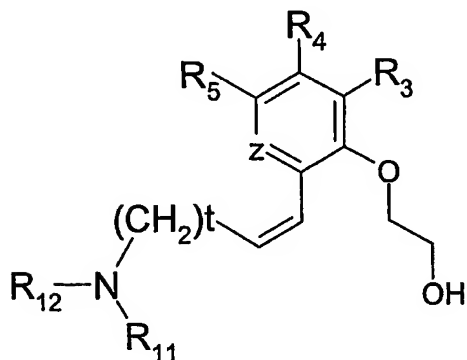
wherein:

R_3 - R_5 , R_{11} , R_{12} , t , and Z are as defined above;



Formula (XXIV)

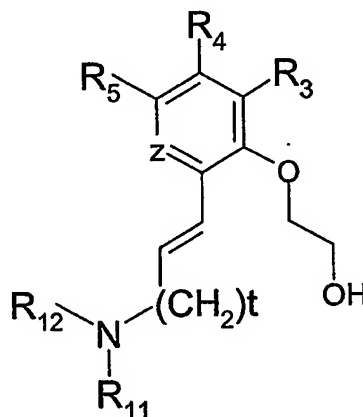
e) treating the compounds of Formula (XXIII) and (XXIV), respectively, with an aqueous acid such as aqueous acetic acid or aqueous hydrochloric acid, to give compounds of Formula (XXV) and (XXVI), respectively:



Formula (XXV)

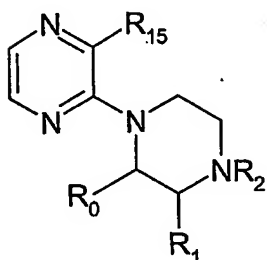
wherein:

R₃-R₅, R₁₁, R₁₂, t, and Z are as defined above;



Formula (XXVI)

f) reacting the compounds of Formula (XXV) and (XXVI) with a compound of Formula (VIII) in the presence of a base, such as potassium tert-butoxide, in a solvent, such as N,N-dimethylformamide:



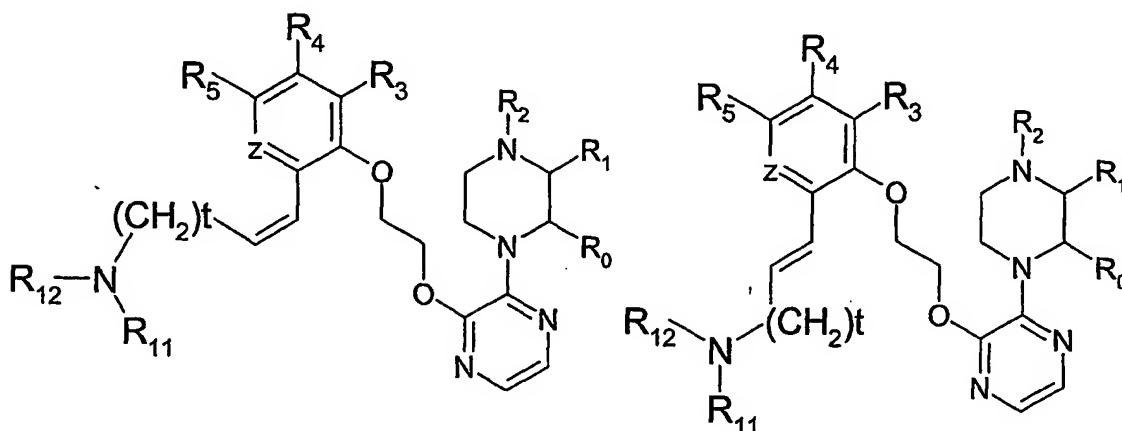
Formula (VIII)

wherein

R₀ and R₁ are each independently H or CH₃;

R₂ is selected from C₁-C₄-alkoxycarbonyl, benzyl, trityl, C₁-C₄-alkyl, 2-hydroxyethyl, 2-cyanoethyl, tetrahydropyran-2-yl, and C₁-C₄-acyl,

R_{15} is halogen, such as chlorine, to give compounds of Formula (XXVII) and (XXVIII):



5 Formula (XXVII)

Formula (XXVIII)

wherein:

R_0 - R_5 , R_{11} , R_{12} , t , and Z are as defined above;

wherein the compounds of Formula (XXVII) and (XXVIII) are isomers of the compound of Formula (Ic) wherein $X = N$ and $Y = N$;

10

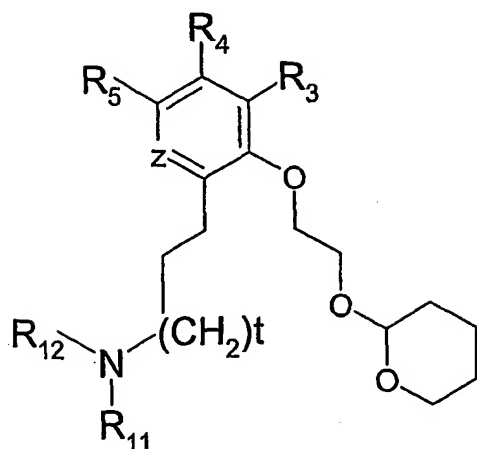
g) if R_2 in Formula (Ic) following step f) is a nitrogen protecting group, such as *t*-BOC, trityl, and benzyl, removing said nitrogen protecting group, such as under acidic conditions (e.g. trifluoroacetic acid in a solvent such as chloroform), hydrogenolytic or non-hydrogenolytic conditions, to provide the compound of Formula (Ic), wherein R_2 is hydrogen.

15

Another object of the present invention is a process for the preparation of a compound of the Formula (Id), which process comprises:

a) treating the compound of Formula (XXII) with hydrogen in the presence of a

20 hydrogenation catalyst, such palladium on carbon, in a solvent, such as methanol, to give a compound of Formula (XXIX):

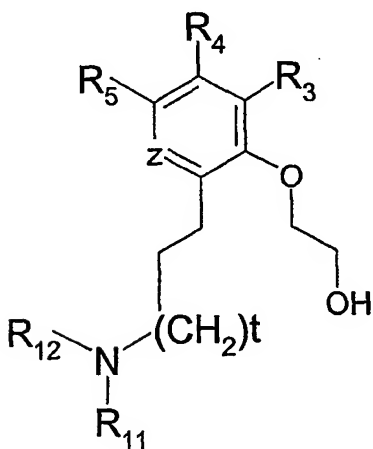


Formula (XXIX)

wherein:

- 5 R_3 - R_5 are each independently H, halogen, methyl, and methoxy, provided that at least one of R_3 - R_5 is hydrogen,
 Z is CH or N,
 t is an integer 1-11, preferably 1-8, more preferably 1-6, most preferably 1; and
 R_{11} and R_{12} are each independently H or straight or branched C_1 - C_4 -alkyl; or R_{11} and R_{12} form
 10 together with the nitrogen atom to which they are attached a saturated heterocyclic ring;

b) treating the compound of Formula (XXIX) with an aqueous acid such as aqueous acetic acid or aqueous hydrochloric acid, to give a compound of Formula (XXX):

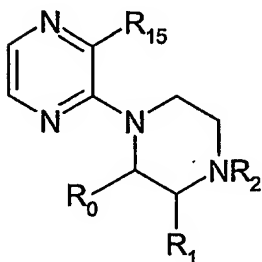


Formula (XXX)

wherein:

R₃-R₅, R₁₁, R₁₂, t, and Z are as defined above;

- c) reacting the compound of Formula (XXX) with a compound of Formula (VIII) in the presence of a base, such as potassium tert-butoxide, in a solvent, such as N,N-dimethylformamide or dioxane:



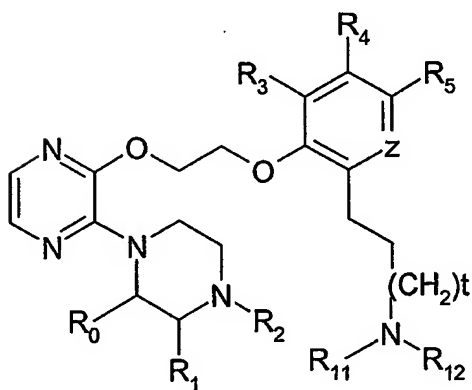
10 Formula (VIII)

wherein

R₀ and R₁ are each independently H or CH₃;

R₂ is selected from C₁-C₄-alkoxycarbonyl, benzyl, trityl, C₁-C₄-alkyl, 2-hydroxyethyl, 2-cyanoethyl, tetrahydropyran-2-yl, and C₁-C₄-acyl,

- 15 R₁₅ is halogen, such as chlorine, to give a compound of Formula (XXXI):



Formula (XXXI):

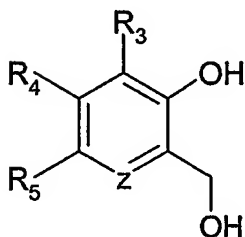
20 wherein:

R₀-R₅, R₁₁, R₁₂, t, and Z are as defined above; wherein Formula (XXXI) corresponds to Formula (Id) wherein W = CH₂, r = t, X = N, Y = N, R₁₃ = R₁₁, and R₁₄ = R₁₂,

- d) if R_2 in Formula (Id) following step c) is a nitrogen protecting group, such as *t*-BOC, trityl, and benzyl, removing said nitrogen protecting group, such as under acidic conditions (e.g. trifluoroacetic acid in a solvent such as chloroform), hydrogenolytic or non-hydrogenolytic conditions, to provide the compound of Formula (Id), wherein R_2 is hydrogen.

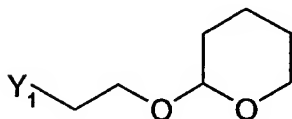
Another object of the present invention is a process for the preparation of a compound of the Formula (Id), which process comprises:

- a) reacting a compound of Formula (XVIII):



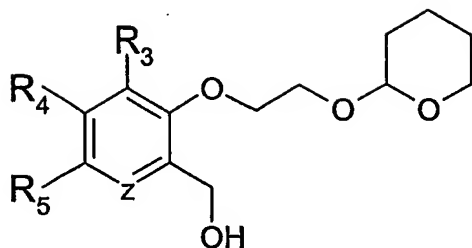
Formula (XVIII)

- wherein:
 R_3 - R_5 are each independently H, halogen, methyl or methoxy, provided that at least one of R_3 - R_5 is hydrogen;
 Z is CH or N,
 with a compound of Formula (III):



Formula (III)

- wherein Y_1 is a suitable leaving group selected from Cl, Br, I, OTs, or OMs;
 in the presence of a base, such as potassium carbonate, triethylamine, or pyridine, in a solvent, such as acetonitrile, to give a compound of Formula (XIX):

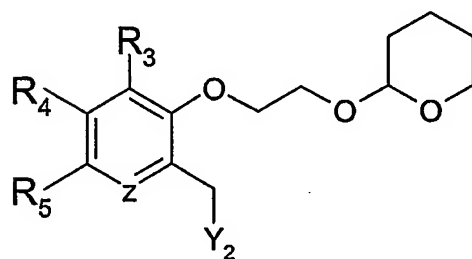


Formula (XIX)

wherein R_3 - R_5 and Z are as defined above,

5

b) transforming the alcohol function in Formula (XIX) into a suitable leaving group, e.g. by treatment with methanesulfonic anhydride in the presence of triethylamine in dichloromethane, to give a compound of Formula (XXXII):



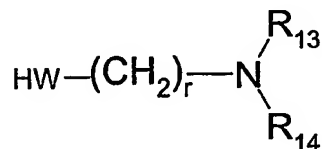
10

Formula (XXXII)

wherein R_3 - R_5 , and Z are as defined above;

Y_2 is halogen, OMs, or OTs;

15 c) reacting the compound of Formula (XXXII) with a compound of Formula (XXXIII) in the presence of a base, such as potassium tert-butoxide, in a solvent, such as dioxane:



20 Formula (XXXIII)

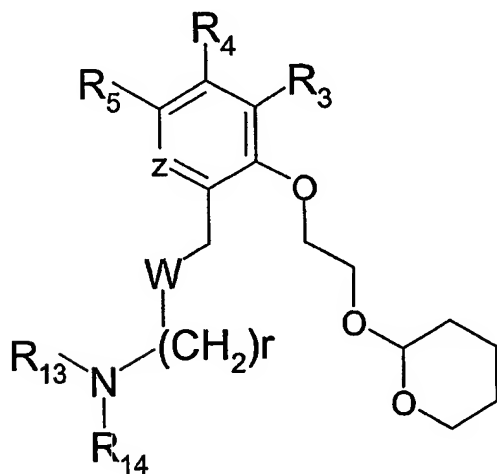
wherein:

W is O;

r is an integer of 1-11, preferably 1-8, more preferably 1-6, most preferably 2;

R₁₃ and R₁₄ are each independently H or straight or branched C₁-C₄-alkyl; or R₁₃ and R₁₄ form together with the nitrogen atom to which they are attached a saturated heterocyclic ring, to give a compound of Formula (XXXIV):

5

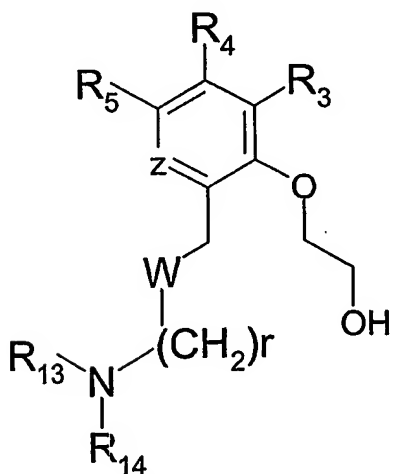


Formula (XXXIV)

wherein:

10 r, z, W, R₃-R₅, and R₁₃ and R₁₄ are as described above;

d) treating the compound of Formula (XXXIV) with an aqueous acid such as aqueous acetic acid or aqueous hydrochloric acid, to give a compound of Formula (XXXV):



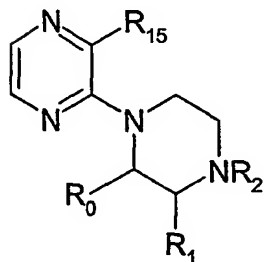
15

Formula (XXXV)

wherein:

r, z, W, R₃-R₅, and R₁₃ and R₁₄ are as described above;

- 5 e) reacting the compound of Formula (XXXV) with a compound of Formula (VIII) in the presence of a base, such as potassium tert-butoxide, in a solvent, such as N,N-dimethylformamide:



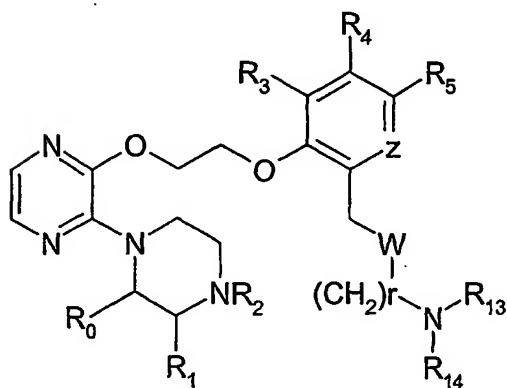
- 10 Formula (VIII)

wherein

R₀ and R₁ are each independently H or CH₃;

R₂ is selected from C₁-C₄-alkoxycarbonyl, benzyl, trityl, C₁-C₄-alkyl, 2-hydroxyethyl, 2-cyanoethyl, tetrahydropyran-2-yl, and C₁-C₄-acyl,

- 15 R₁₅ is halogen, such as chlorine, to give a compound of Formula (XXXVI):



Formula (XXXVI):

- 20 wherein:

R₀-R₅, R₁₃, R₁₄, r, W, and Z are as defined above; wherein Formula (XXXVI) corresponds to Formula (Id) wherein X = N and Y = N,

f) if R_2 in Formula (Id) following step e) is a nitrogen protecting group, such as *t*-BOC, trityl, and benzyl, removing said nitrogen protecting group, such as under acidic conditions (e.g. trifluoroacetic acid in a solvent such as chloroform), hydrogenolytic or non-hydrogenolytic conditions, to provide the compound of Formula (Id), wherein R_2 is hydrogen.

The chemicals used in the above-described synthetic routes may include, for example, solvents, reagents, catalysts, protecting group and deprotecting group agents. The methods described above may also additionally include steps, either before or after the steps described specifically herein, to add or remove suitable protecting groups in order to ultimately allow synthesis of the compounds of Formulae (I). In addition, various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing applicable compounds are known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof. Examples of protecting groups according to the present invention are *t*-BOC (tert-butoxycarbonyl), trityl, and benzyl.

It should be noted that a compound of Formula (I) (including any of Formulae Ia, Ib, Ic and Id) as prepared according to the present invention may be converted to another compound of Formula (I) by methods well known in the art. For example, a standard reductive alkylation reaction is illustrated in Example 17 by the preparation of a compound of Formula (I) wherein R_2 is methyl from the corresponding compound of Formula (I) wherein R_2 is hydrogen (cf. the protocol described in J. Org. Chem. 1996, 61, 3849-3862).

The processes described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. A pharmaceutically acceptable acid addition salt may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Examples of addition salt forming acids are maleic acid, fumaric acid, succinic acid, methanesulfonic acid, trifluoroacetic acid, acetic acid, oxalic

acid, benzoic acid, malic acid, hydrochloric acid, sulphuric acid, phosphoric acid, isethionic acid, and the like.

The compounds of Formulae (I) may possess one or more chiral carbon atoms, and they may therefore be obtained in the form of optical isomers, e.g. as a pure enantiomer, or as
5 a mixture of enantiomers (racemate) or as a mixture containing diastereomers. The separation of mixtures of optical isomers to obtain pure enantiomers is well known in the art and may, for example, be achieved by fractional crystallization of salts with optically active (chiral) acids or by chromatographic separation on chiral columns.

The necessary starting materials for preparing the compounds of Formulae (I) are
10 either known or may be prepared in analogy with the preparation of known compounds.

In accordance with the present invention, the compounds of Formulae (I), in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical
15 compositions according to the invention comprise an effective amount of the compounds of Formulae (I) in association with compatible pharmaceutically acceptable carrier materials, or diluents, as are well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous, subcutaneous or parenteral administration, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch
20 glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmacologically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

The compositions according to the invention can e.g. be made up in solid or liquid
25 form for oral administration, such as tablets, pills, capsules, powders, syrups, elixirs, dispersable granules, cachets, suppositories and the like, in the form of sterile solutions, suspensions or emulsions for parenteral administration, sprays, e.g. a nasal spray, transdermal preparations, e.g. patches, and the like.

As mentioned above, the compounds of the invention may be used for the treatment of
30 a human or animal subject suffering from a serotonin-related disorder or condition, particularly 5-HT_{2C} receptor-related, such as memory disorders, such as Alzheimer's disease; schizophrenia; mood disorders such as depression; anxiety disorders; pain; substance abuse; sexual dysfunctions such as erectile dysfunction; epilepsy; glaucoma; urinary disorders, such as urinary incontinence; menopausal and post-menopausal hot flushes; type 2 diabetes; eating

disorders, such as binge eating disorders, anorexia nervosa and bulimia; weight gain associated with antipsychotic drug administration, premenstrual tension, sleep disorders; and particularly obesity.

This invention also relates to a method of treatment or prophylaxis of a serotonin-related disorder or condition as described above. The method includes administering to a
5 subject (e.g., a human, a horse, a dog, or a cat) in need thereof an effective amount of one or more compounds of Formulae (I) described above. The methods delineated herein can also include the step of identifying that the subject is in need of treatment of the serotonin-related disorder or condition.

Also within the scope of this invention is a method for modulating (e.g., stimulating or inhibiting) 5-HT_{2C} receptor function. The method includes contacting the receptor with an effective stimulatory or inhibitory amount of a compound of Formula (I), preferably an effective stimulatory amount thereof. The contacting step can include administering a compound, its salt, or a composition containing the compound or the salt.

“An effective amount” refers to an amount of a compound which confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). The dose level and frequency of dosage of the specific compound will vary depending on a variety of factors including the potency of the specific compound employed, the metabolic stability
20 and length of action of that compound, the patient's age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the condition to be treated, and the patient undergoing therapy. The daily dosage may, for example, range from about 0.001 mg to about 100 mg per kilo of body weight, administered singly or multiply in doses, e.g. from about 0.01 mg to about 25 mg each. Normally, such a
25 dosage is given orally but parenteral administration may also be chosen.

The invention will now be further illustrated by the following non-limiting Examples. Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. All publications cited herein are hereby incorporated by reference in their entirety.

EXAMPLESGeneral.

Unless otherwise noted, starting materials were obtained from commercial sources and
5 used as received. ^1H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were
recorded on a Bruker Advance DPX 400 spectrometer at 400.1 and 100.6 MHz,
respectively, or on a JEOL 270 spectrometer. All spectra were recorded using residual
solvent as internal standard. Melting points were determined with a Kofler bench and
are uncorrected. Electrospray mass spectrometry (MS) spectra were obtained on a
10 Perkin-Elmer API 150EX mass spectrometer. Accurate mass measurements were
performed on a Micromass LCT dual probe.

HPLC (high-performance liquid chromatography) conditions for Example 1 and
Example 2:

15 The preparative LC was performed on a preparative LC-MS Gilson-Finnigan with a
50x20mm S 5 μm , 120A column. The flow was 30 mL/min and different gradients of 0.1%
acetic acid in water and acetonitrile were used.

HPLC conditions for Examples 3-16: Preparative HPLC was performed on a Gilson-system
20 equipped with an YMC AQ C18, 5 μm column (20x50mm), eluent: water/acetonitrile + 0.1%
trifluoroacetic acid. Analytical LC-UV was performed on an Agilent 1100 system with an
ACE C8, 3 μm column (3x50 mm), eluent: water/acetonitrile + 0.1% trifluoroacetic acid.
Analytical LC-MS was performed on an Agilent 1100 system with an YMC AQ C18, 3 μm
column (3x33 mm), eluent: water/acetonitrile + 0.1% trifluoroacetic acid.

25

HPLC conditions for Examples 17-27: Preparative HPLC/MS was performed on a
Waters/Micromass Platform ZQ system equipped with System A: ACE 5 C8 column
(19x50mm), eluent: 0.1% TFA in different gradients of MilliQ water and MeCN.
System B: Xterra MS C18, 5 μm column (19x50mm), eluent: 10 mM $\text{NH}_4\text{HCO}_3/\text{NH}_3$
30 buffer pH 10 in different gradients of MilliQ water and MeCN. Analytical HPLC were
performed on Agilent 1100, column: ACE 3 C8 (system A) or column: YMC-Pack
(system B), eluents: MilliQ/0.1%TFA and MeCN. Preparative flash chromatography

was performed on Merck silica gel 60 (230-400 mesh). GC-MS analysis were performed on a Hewlett Packard 5890 gas chromatograph with a HP-5MS 15 m x 0.25 mm x 0.25 μ m column connected to a 5971 MS detector.

5 EXAMPLE 1

N,N-Dimethyl-(2-(3-[2-(2-(*R*)-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrazinyl-3'-yloxy)-ethoxy]-pyridin-2-yloxy)-ethyl)-amine, acetate.

Step 1: 3-Benzoyloxy-2-bromopyridine*

A mixture of 2-bromo-pyridine-3-ol (50.4 g, 0.29 mol), benzyl bromide (45.5 g, 0.28
10 mol) and potassium carbonate (52 g, 0.38 mol) in dry *N,N*-dimethylformamide (DMF; 300 mL) was heated at 110 °C for 30 minutes. The mixture was filtered through a pad of Celite®, the solvent was removed under reduced pressure and the black residue was taken up between ice cold 0.5 M aqueous NaOH and EtOAc. The organic phase was washed twice with brine, dried (MgSO₄), and concentrated under reduced pressure to yield 69.6 g (93%) of the title
15 compound as a brown oil. HRMS *m/z* calcd for C₁₂H₁₀BrNO (M)⁺ 263.9946, found 263.9939.
*Previously described in J. Med. Chem. 1996, 39, 5267-5275.

Step 2: 2-[[3-(Benzoyloxy)pyridin-2-yl]oxy]-*N,N*-dimethylethanamine.

To a mixture of *N,N*-dimethylaminoethanol (4.16 g, 46.7 mmol) and (3-benzoyloxy)-2-
20 bromopyridine (from Step 1; 8.22 g, 31.1 mmol) in dry DMF (50 mL) was sodium *tert*-butoxide (5.98 g, 62.2 mmol) added in one portion. The reaction mixture was stirred at 80 °C for 1.5 h, the solvent was removed under reduced pressure and the oily residue was taken up between CHCl₃/water. The aqueous phase was extracted twice with CHCl₃ and the combined organic layers were washed once with brine, dried (MgSO₄), and concentrated under reduced
25 pressure. This gave 8.4 g (100%) of the title compound as a light brown oil. Purity 95% (HPLC). HRMS *m/z* calcd for C₁₆H₂₀N₂O₂ (M)⁺ 272.1525, found 272.1537.

Step 3: 2-[2-(2-Dimethylamino-ethoxy)-pyridine-3-yloxy]-ethanol.

To a N₂-flushed solution of 2-[[3-(benzoyloxy)pyridin-2-yl]oxy]-*N,N*-
30 dimethylethanamine (from Step 2; 8.4 g, 31.1 mmol) in MeOH (100 mL) was added 10% Pd/C (0.8 g) followed by ammonium formate (6.3 g, 100 mmol). The mixture was stirred at 50 °C under an atmosphere of nitrogen for 2 h. The reaction was filtered through Celite® and the solvent was removed under reduced pressure to yield a semi-crystalline material that was

used without further purification in the next synthetic step. The crude product was dissolved in dry DMF (50 mL), potassium carbonate (6.0 g, 43 mmol) was added and the mixture was heated at 150 °C for 20 minutes. Ethylene carbonate (4.1 g, 46 mmol) was added and the heating was continued for another 1.5 h. Solids were filtered off and the filtrate was concentrated under reduced pressure. The residue was chromatographed on a column of silica using CHCl₃/MeOH/NH₄OH (95:5:0.2) as eluent to give 3.28 g (31%) of the title product as a light brown oil. HRMS *m/z* calcd for C₁₁H₁₈N₂O₃ (M)⁺ 226.1317, found 226.1323.

Step 4: *N,N*-Dimethyl-(2-(3-[2-(2-(*R*)-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrazinyl-3'-yloxy)-ethoxy]-pyridin-2-yloxy)-ethyl)-amine, acetate.

To a solution of 2-[2-(2-dimethylamino-ethoxy)-pyridine-3-yloxy]-ethanol (from Step 3; 2.89 g, 12.8 mmol) in DMF (50 mL) was sodium *tert*-butoxide (1.84 g, 19.2 mmol) added in one portion and the reaction was stirred at room temperature for 10 minutes. To the mixture was (2*R*)-1-(3-chloro-2-pyrazinyl)-2-methylpiperazine* (2.81 g, 13.5 mmol) added and the reaction was stirred at 60 °C for 30 minutes. Silica (~15 g) was added and the mixture was filtered through a short plug of silica. The solvent was evaporated under reduced pressure and the residue was chromatographed on a column of silica using CHCl₃/MeOH/NH₄OH (95:5:0.2 followed by 90:10:0.2) as eluent. The solvent from the pure combined fractions was evaporated off under reduced pressure and the residue was dissolved in ether and HOAc in ether was added. After 15 h in the refrigerator white crystals could be filtered off and dried (60 °C, 1 mm Hg) to give 2.5 g (42%) of the title compound: mp 75 °C. Fragmenting MS analysis supports the stated structure. HRMS *m/z* calcd for C₂₀H₃₀N₆O₃ (M)⁺ 402.2379, found 402.2383. *Prepared as described in WO 00/76984, Example 192, Step 2.

EXAMPLE 2

***N,N*-Diisopropyl-(2-(3-[2-(2-(*R*)-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrazinyl-3'-yloxy)-ethoxy]-pyridin-2-yloxy)-ethyl)-amine, acetate.**

Step 1: (2-{[3-(Benzyloxy)pyridin-2-yl]oxy}ethyl)diisopropylamine.

To a mixture of *N,N*-diisopropylaminoethanol (4.07 g, 28.0 mmol) and (3-benzyloxy)-2-bromopyridine (from Example 1, Step 1; 6.16 g, 23.3 mmol) in dry DMF (50 mL) was sodium *tert*-butoxide (3.36 g, 35.0 mmol) added in one portion. The reaction mixture was stirred at 80 °C for 1.5 h. Silica (~15 g) was added and the mixture was filtered. The solvent was evaporated off under reduced pressure and the remaining oil was chromatographed on a column of silica using toluene/Et₃N (97:3) as eluent to give 5.8 g (76%) of the title compound

as a light brown oil. Purity 85% (HPLC). Fragmenting MS analysis supports the stated structure. HRMS m/z calcd for $C_{20}H_{28}N_2O_2 (M)^+$ 328.2151, found 328.2142.

Step 2: 2-[2-(2-Diisopropylamino-ethoxy)-pyridine-3-yloxy]-ethanol.

The title compound was prepared starting from 2-[[3-(benzyloxy)pyridin-2-yl]oxy]ethyl)diisopropylamine (from Step 1; 5.0 g, 15.2 mmol) using the procedure given in Example 1, Step 3. This produced 1.8 g (42%) of the title compound as a light brown oil. Purity 91% (HPLC). Fragmenting MS analysis supports the stated structure. HRMS m/z calcd for $C_{15}H_{26}N_2O_3 (M)^+$ 282.1943, found 282.1948.

Step 3: *N,N*-Diisopropyl-(2-(3-[2-(2-(*R*)-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrazinyl-3'-yloxy)-ethoxy]-pyridin-2-yloxy)-ethyl)-amine, acetate.

The title compound was prepared starting from 2-[2-(2-diisopropylamino-ethoxy)-pyridine-3-yloxy]-ethanol (1.52 g, 5.30 mmol) and (2*R*)-1-(3-chloro-2-pyrazinyl)-2-methylpiperazine* (1.24 g, 5.83 mmol) using the procedure given Example 1, Step 4. The crude product was chromatographed on a column of silica using $CHCl_3/MeOH/aqueous$ concentrated NH_3 (90:10:0.2 followed by 80:20:0.3) as the eluent. The solvent from the pure combined fractions was evaporated off under reduced pressure, the residue was dissolved in ether, and HOAc in ether was added. After 15 h in the refrigerator, white crystals were collected by filtration and dried (60 °C, 1 mm Hg) to give 1.5 g (56%) of the title compound: mp 87 °C. Purity 99% (HPLC). Fragmenting HPLC analysis supports the stated structure. HRMS m/z calcd for $C_{24}H_{38}N_6O_3 (M)^+$ 458.3005, found 458.2988. *Prepared as described in WO 00/76984, Example 192, Step 2.

EXAMPLE 3

***N,N*-Dimethyl-2-[(3-{2-[(3-piperazin-1-ylpyrazin-2-yl)oxy]ethoxy}pyridin-2-yl)oxy]ethanamine, trifluoroacetate.**

To a solution of *tert*-butyl 4-(3-chloropyrazin-2-yl)piperazine-1-carboxylate* (45 mg, 0.15 mmol) and 2-({2-[2-(dimethylamino)ethoxy]pyridin-3-yl}oxy)ethanol (from Example 1, Step 3; 37 mg, 0.16 mmol) in 4 mL of dry methyl *tert*-butyl ether was 0.2 mL of 1.0 M potassium *tert*-butoxide in *tert*-butanol added and the mixture was stirred at room temperature for one week. The reaction mixture was quenched with 2 mL of water. The organic phase was washed with 3 x 2 mL of 1.0 M NaOH and 2 mL of brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified with reversed phase chromatography. The purified

product was concentrated, redissolved in 3 mL of chloroform, and treated with 0.2 mL of trifluoroacetic acid overnight. The solvent was removed under reduced pressure to give 46 mg (0.092 mmol, 61%) of the title compound as an oil. LC-UV purity 100%. HRMS m/z calc for $C_{19}H_{28}N_6O_3$ (M)⁺ 388.2223, found 388.2217. * Prepared as described in WO 00/76984,

5 Example 52, Step 1.

EXAMPLE 4 (intermediate)

2-Chloro-3-[2-(tetrahydro-2H-pyran-2-yloxy)ethoxy]pyridine.

A mixture of 2-chloro-3-hydroxypyridine (5.00 g, 38.6 mmol), 2-(2-bromoethoxy)tetrahydro-
10 2-pyran (5.85 mL, 38.6 mmol) and potassium carbonate (6.40 g, 46.3 mmol) in 200 mL of acetonitrile was heated at reflux overnight. The reaction mixture was filtered, concentrated under reduced pressure and redissolved in 300 mL of ethyl acetate. The organic phase was washed with 3 x 100 mL of NaOH and 100 mL of brine, dried (MgSO₄) and concentrated under reduced pressure. The residue was purified with flash chromatography on a column of
15 silica to give 7.21 g (28.0 mmol, 73%) of the title compound as a yellow oil. LC-UV purity 100%. MS m/z 258 (M+1)⁺, calc. 258 (M+1)⁺.

EXAMPLE 5 (intermediate)

tert-Butyl (3*R*)-4-(3-chloropyrazin-2-yl)-3-methylpiperazine-1-carboxylate.*

20 To a solution of 2-chloro-3-[(2*R*)-2-methylpiperazin-1-yl]pyrazine** (1.59 g, 7.48 mmol) in 200 mL of acetonitrile was boc-anhydride (1.63 g, 7.48 mmol) added in portions over 1 hour. The solution was stirred at room temperature overnight, quenched with 10 mL of water and concentrated. The residue was redissolved in 200 mL of ethyl acetate, washed with 100 mL of 1.0 M K₂CO₃, 100 mL of water and 100 mL of brine, dried (MgSO₄) and concentrated to give
25 1.70 g (5.43 mmol, 73%) of the title compound as a colorless oil. LC-UV purity 95%. MS m/z 313 (M+1)⁺, calc. 313 (M+1)⁺. *Reported in WO 00/76984, Example 172, Step 2. **Reported in WO 00/76984, Example 192, Step 2.

EXAMPLE 6

30 2-[(2*R*)-2-Methylpiperazin-1-yl]-3-[2-({2-[(1-methylpiperidin-4-yl)oxy]pyridin-3-yl}oxy)ethoxy]pyrazine, trifluoroacetate.

Step 1: 2-({2-[(1-Methylpiperidin-4-yl)oxy]pyridin-3-yl}oxy)ethanol.

A solution of 2-chloro-3-[2-(tetrahydro-2H-pyran-2-yloxy)ethoxy]pyridine (from Example 4; 100 mg, 0.39 mmol), 4-hydroxy-*N*-methylpiperidine (67 μ l, 0.58 mmol) and 1.0 M potassium

tert-butoxide in *tert*-butanol (0.8 mL, 0.80 mmol) in 4 mL of toluene was heated at 100 °C for 1 day. The organic phase was washed with 3 x 2 mL of water and 2 mL of brine. The organic phase was shaken at 50 °C with 4 mL of 2.0 M acetic acid for 2 days. The aqueous phase was washed with 3 x 3 mL of ethyl acetate, made basic by addition of potassium hydroxide, saturated with sodium chloride and extracted with 3 x 2 mL of ethyl acetate. The organic phase was dried (MgSO₄) and concentrated under reduced pressure to give 62 mg (0.25 mmol, 63%) of the title compound as a colorless oil. LC-UV purity 95%. MS *m/z* 253 (M+1)⁺, calc. 253 (M+1)⁺.

10 Step 2: 2-[(2*R*)-2-Methylpiperazin-1-yl]-3-[2-({2-[(1-methylpiperidin-4-yl)oxy]pyridin-3-yl}oxy)ethoxy]pyrazine, trifluoroacetate.

To a solution of 2-({2-[(1-methylpiperidin-4-yl)oxy]pyridin-3-yl}oxy)ethanol (from Step 1; 30 mg, 0.12 mmol) and 1.0 M potassium *tert*-butoxide in *tert*-butanol (0.15 mL, 0.15 mmol) in 4 mL of dry toluene was *tert*-butyl (3*R*)-4-(3-chloropyrazin-2-yl)-3-methylpiperazine-1-carboxylate (from Example 5; 31 mg, 0.10 mmol) in 1 mL of toluene added. The mixture was shaken at room temperature for 2 days. The reaction mixture was quenched with 2 mL of water. The organic phase was washed with 3 x 2 mL of water and 2 mL of brine and concentrated under reduced pressure. The residue was purified with reversed phase chromatography. The purified product was concentrated, redissolved in 1 mL of chloroform and treated with 0.2 mL of trifluoroacetic acid for 1 hour. The solvent was removed under reduced pressure to give 36 mg (0.066 mmol, 66%) of the title compound as a brown oil. LC-UV purity 100%. HRMS *m/z* calcd for C₂₂H₃₂N₆O₃ (M)⁺ 428.2536, found 428.2546.

EXAMPLE 7

25 2-[(2*R*)-2-Methylpiperazin-1-yl]-3-(2-{[2-(2-pyrrolidin-1-ylethoxy)pyridin-3-yl]oxy}ethoxy)pyrazine, trifluoroacetate.

Step 1: 2-{[2-(2-Pyrrolidin-1-ylethoxy)pyridin-3-yl]oxy}ethanol.

A solution of 2-chloro-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]pyridine (from Example 4; 100 mg, 0.39 mmol), 1-(2-hydroxyethyl)pyrrolidine (68 µL, 0.58 mmol) and 1.0 M potassium *tert*-butoxide in *tert*-butanol (0.8 mL, 0.80 mmol) in 4 mL of toluene was heated at 100 °C for 1 day. The organic phase was washed with 3 x 2 mL of water and 2 mL of brine. The organic phase was shaken at 50 °C with 4 mL of 2.0 M acetic acid for 2 days. The aqueous phase was washed with 3 x 3 mL of ethyl acetate, made basic by addition of potassium hydroxide, saturated with sodium chloride and extracted with 3 x 2 mL of ethyl acetate. The organic

phase was dried (MgSO₄) and concentrated under reduced pressure to give 71 mg (0.28 mmol, 72%) of the title compound as a colorless oil. LC-UV purity 95%. MS *m/z* 253 (M+1)⁺, calc. 253 (M+1)⁺.

5 **Step 2: 2-[(2*R*)-2-Methylpiperazin-1-yl]-3-(2-{[2-(2-pyrrolidin-1-ylethoxy)pyridin-3-yl]oxy}ethoxy)pyrazine, trifluoroacetate.**

The procedure in Example 6, Step 2, was followed using 2-{[2-(2-pyrrolidin-1-ylethoxy)pyridin-3-yl]oxy}ethanol (from Step 1; 36 mg, 0.14 mmol) to give 37 mg (0.069 mmol, 69%) of the title compound as a brown oil. LC-UV purity 100%. HRMS *m/z* calcd for
10 C₂₂H₃₂N₆O₃ (M)⁺ 428.2536, found 428.2551.

EXAMPLE 8

***N,N*-Dimethyl-4-({3-[2-({3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl]oxy}ethoxy)pyridin-2-yl]oxy)butan-1-amine, trifluoroacetate.**

15 **Step 1: 2-({2-[4-(Dimethylamino)butoxy]pyridin-3-yl}oxy)ethanol.**

A solution of 2-chloro-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]pyridine (from Example 4; 100 mg, 0.39 mmol), 4-(dimethylamino)-1-butanol (77 μ l, 0.58 mmol) and 1.0 M potassium *tert*-butoxide in *tert*-butanol (0.8 mL, 0.80 mmol) in 4 mL of toluene was heated at 100 °C for 1 day. The organic phase was washed with 3 x 2 mL of water and 2 mL of brine. The organic
20 phase was shaken at 50 °C with 4 mL of 2.0 M acetic acid for 2 days. The aqueous phase was washed with 3 x 3 mL of ethyl acetate, made basic by addition of potassium hydroxide, saturated with sodium chloride and extracted with 3 x 2 mL of ethyl acetate. The organic phase was dried (MgSO₄) and concentrated under reduced pressure to give 55 mg (0.22 mmol, 55%) of the title compound as a colorless oil. LC-UV purity 95%. MS *m/z* 255
25 (M+1)⁺, calc. 255 (M+1)⁺.

Step 2: *N,N*-Dimethyl-4-({3-[2-({3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl]oxy}ethoxy)pyridin-2-yl]oxy)butan-1-amine, trifluoroacetate.

The procedure in Example 6, Step 2, was followed using 2-({2-[4-(dimethylamino)butoxy]pyridin-3-yl}oxy)ethanol (from Step 1; 29 mg, 0.11 mmol) to give 34
30 mg (0.062 mmol, 62%) of the title compound as a brown oil. LC-UV purity 100%. HRMS *m/z* calcd for C₂₂H₃₄N₆O₃ (M)⁺ 430.2692, found 430.2695.

EXAMPLE 9

2-[(2*R*)-2-Methylpiperazin-1-yl]-3-[2-({2-[2-(1-methylpyrrolidin-2-yl)ethoxy]pyridin-3-yl}oxy)ethoxy]pyrazine, trifluoroacetate.

Step 1: 2-({2-[2-(1-Methylpyrrolidin-2-yl)ethoxy]pyridin-3-yl}oxy)ethanol.

A solution of 2-chloro-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]pyridine (from Example 4;

- 5 100 mg, 0.39 mmol), 1-methyl-2-pyrrolidineethanol (79 μ l, 0.58 mmol) and 1.0 M potassium *tert*-butoxide in *tert*-butanol (0.8 mL, 0.80 mmol) in 4 mL of toluene was heated at 100 °C for 1 day. The organic phase was washed with 3 x 2 mL of water and 2 mL of brine. The organic phase was shaken at 50 °C with 4 mL of 2.0 M acetic acid for 2 days. The aqueous phase was washed with 3 x 3 mL of ethyl acetate, made basic by addition of potassium hydroxide,
- 10 saturated with sodium chloride and extracted with 3 x 2 mL of ethyl acetate. The organic phase was dried (MgSO₄) and concentrated under reduced pressure to give 55 mg (0.21 mmol, 53%) of the title compound as a colorless oil. LC-UV purity 95%. MS *m/z* 267 (M+1)⁺, calc. 267 (M+1)⁺.

- 15 **Step 2:** 2-[(2*R*)-2-Methylpiperazin-1-yl]-3-[2-({2-[2-(1-methylpyrrolidin-2-yl)ethoxy]pyridin-3-yl}oxy)ethoxy]pyrazine, trifluoroacetate.

The procedure in Example 6, Step 2, was followed using 2-({2-[2-(1-methylpyrrolidin-2-yl)ethoxy]pyridin-3-yl}oxy)ethanol (from Step 1; 28 mg, 0.11 mmol) to give 33 mg (0.059 mmol, 59%) of the title compound as a brown oil. LC-UV purity 100%. HRMS *m/z* calcd for C₂₃H₃₄N₆O₃ (M)⁺ 442.2692, found 442.2681.

- 20

EXAMPLE 10

N-Methyl-*N*-[2-({3-[2-({3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)ethyl]propan-2-amine, trifluoroacetate.

- 25 **Step 1:** 2-[(2-{2-[Isopropyl(methyl)amino]ethoxy}pyridin-3-yl)oxy]ethanol.

A solution of 2-chloro-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]pyridine (from Example 4; 100 mg, 0.39 mmol), 2-(*N*-methyl-*N*-isopropylamino)ethanol (68 μ l, 0.58 mmol) and 1.0 M potassium *tert*-butoxide in *tert*-butanol (0.8 mL, 0.80 mmol) in 4 mL of toluene was heated at 100 °C for 1 day. The organic phase was washed with 3 x 2 mL of water and 2 mL of brine.

- 30 The organic phase was shaken at 50 °C with 4 mL of 2.0 M acetic acid for 2 days. The aqueous phase was washed with 3 x 3 mL of ethyl acetate, made basic by addition of potassium hydroxide, saturated with sodium chloride and extracted with 3 x 2 mL of ethyl acetate. The organic phase was dried (MgSO₄) and concentrated under reduced pressure to

give 75 mg (0.30 mmol, 76%) of the title compound as a colorless oil. LC-UV purity 95%. MS m/z 255 (M+1)⁺, calc. 255 (M+1)⁺.

Step 2: *N*-Methyl-*N*-[2-({3-[2-({3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)ethyl]propan-2-amine, trifluoroacetate.

The procedure in Example 6, Step 2, was followed using 2-[(2-{[isopropyl(methyl)amino]ethoxy}pyridin-3-yl)oxy]ethanol (from Step 1; 40 mg, 0.16 mmol) to give 38 mg (0.070 mmol, 70%) of the title compound as a brown oil. LC-UV purity 100%. HRMS m/z calcd for C₂₂H₃₄N₆O₃ (M)⁺ 430.2692, found 430.2700.

EXAMPLE 11

***N,N*-Dimethyl-3-({3-[2-({3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)propan-1-amine, trifluoroacetate.**

Step 1: 2-({2-[3-(Dimethylamino)propoxy]pyridin-3-yl}oxy)ethanol.

A solution of 2-chloro-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]pyridine (from Example 4; 100 mg, 0.39 mmol), 3-dimethylamino-1-propanol (69 μ l, 0.58 mmol) and 1.0 M potassium *tert*-butoxide in *tert*-butanol (0.8 mL, 0.80 mmol) in 4 mL of toluene was heated at 100 °C for 1 day. The organic phase was washed with 3 x 2 mL of water and 2 mL of brine. The organic phase was shaken at 50 °C with 4 mL of 2.0 M acetic acid for 2 days. The aqueous phase was washed with 3 x 3 mL of ethyl acetate, made basic by addition of potassium hydroxide, saturated with sodium chloride and extracted with 3 x 2 mL of ethyl acetate. The organic phase was dried (MgSO₄) and concentrated under reduced pressure to give 67 mg (0.28 mmol, 71%) of the title compound as a colorless oil. LC-UV purity 95%. MS m/z 241 (M+1)⁺, calc. 241 (M+1)⁺.

Step 2: *N,N*-Dimethyl-3-({3-[2-({3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)propan-1-amine, trifluoroacetate.

The procedure in Example 6, Step 2, was followed using 2-({2-[3-(dimethylamino)propoxy]pyridin-3-yl}oxy)ethanol (from Step 1; 31 mg, 0.13 mmol) to give 38 mg (0.072 mmol, 72%) of the title compound as a brown oil. LC-UV purity 95%. HRMS m/z calcd for C₂₁H₃₂N₆O₃ (M)⁺ 416.2536, found 416.2523.

EXAMPLE 12

2-[(2*R*)-2-Methylpiperazin-1-yl]-3-(2-{[2-(piperidin-3-ylmethoxy)pyridin-3-yl]oxy}ethoxy)pyrazine, trifluoroacetate.

Step 1: 2-{[2-(Piperidin-3-ylmethoxy)pyridin-3-yl]oxy}ethanol.

A solution of 2-chloro-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]pyridine (from Example 4; 100 mg, 0.39 mmol), 3-piperidinemethanol (65 μ l, 0.58 mmol) and 1.0 M potassium *tert*-butoxide in *tert*-butanol (0.8 mL, 0.80 mmol) in 4 mL of toluene was heated at 100 °C for 1 day. The organic phase was washed with 3x2 mL of water and 2 mL of brine. The organic phase was shaken at 50 °C with 4 mL of 2.0 M acetic acid for 2 days. The aqueous phase was washed with 3 x 3 mL of ethyl acetate, made basic by addition of potassium hydroxide, saturated with sodium chloride and extracted with 3 x 2 mL of ethyl acetate. The organic phase was dried (MgSO₄) and concentrated under reduced pressure to give 52 mg (0.21 mmol, 53%) of the title compound as a colorless oil. LC-UV purity 95%. MS *m/z* 253 (M+1)⁺, calc. 253 (M+1)⁺.

Step 2: 2-[(2*R*)-2-Methylpiperazin-1-yl]-3-(2-{[2-(piperidin-3-ylmethoxy)pyridin-3-yl]oxy}ethoxy)pyrazine, trifluoroacetate.

The procedure in Example 6, Step 2, was followed using 2-{[2-(piperidin-3-ylmethoxy)pyridin-3-yl]oxy}ethanol (from Step 1; 27 mg, 0.11 mmol) to give 37 mg (0.069 mmol, 69%) of the title compound as a brown oil. LC-UV purity 95%. HRMS *m/z* calcd for C₂₂H₃₂N₆O₃ (M)⁺ 428.2536, found 428.2543.

EXAMPLE 13

***N,N*,2-Trimethyl-1-({3-[2-({3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)propan-2-amine, trifluoroacetate.**

Step 1: 2-{[2-[2-(Dimethylamino)-2-methylpropoxy]pyridin-3-yl]oxy}ethanol.

A solution of 2-chloro-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]pyridine (from Example 4; 100 mg, 0.39 mmol), 2-(dimethylamino)-2-methyl-1-propanol (68 μ l, 0.58 mmol) and 1.0 M potassium *tert*-butoxide in *tert*-butanol (0.8 mL, 0.80 mmol) in 4 mL of toluene was heated at 100 °C for 1 day. The organic phase was washed with 3 x 2 mL of water and 2 mL of brine.

The organic phase was shaken at 50 °C with 4 mL of 2.0 M acetic acid for 2 days. The aqueous phase was washed with 3 x 3 mL of ethyl acetate, made basic by addition of potassium hydroxide, saturated with sodium chloride and extracted with 3 x 2 mL of ethyl acetate. The organic phase was dried (MgSO₄) and concentrated under reduced pressure to

give 79 mg (0.31 mmol, 80%) of the title compound as a colorless oil. LC-UV purity 95%. MS m/z 255 (M+1)⁺, calc. 255 (M+1)⁺.

Step 2: *N,N*,2-Trimethyl-1-({3-[2-({3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)propan-2-amine, trifluoroacetate.

The procedure in Example 6, Step 2, was followed using 2-({2-[2-(dimethylamino)-2-methylpropoxy]pyridin-3-yl}oxy)ethanol (from Step 1; 38 mg, 0.15 mmol) to give 47 mg (0.086 mmol, 86%) of the title compound as a brown oil. LC-UV purity 95%. HRMS m/z calcd for C₂₂H₃₄N₆O₃ (M)⁺ 430.2692, found 430.2700.

EXAMPLE 14

2-[(2*R*)-2-Methylpiperazin-1-yl]-3-{2-[(2-[(2*S*)-1-methylpyrrolidin-2-yl]methoxy}pyridin-3-yl)oxy]ethoxy}pyrazine, trifluoroacetate.

Step 1: 2-[(2-[(2*S*)-1-Methylpyrrolidin-2-yl]methoxy}pyridin-3-yl)oxy]ethanol.

A solution of 2-chloro-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]pyridine (from Example 4; 100 mg, 0.39 mmol), (*S*)-(-)-2-hydroxymethyl-1-methylpyrrolidine (69 μ L, 0.58 mmol) and 1.0 M potassium *tert*-butoxide in *tert*-butanol (0.8 mL, 0.80 mmol) in 4 mL of toluene was heated at 100 °C for 1 day. The organic phase was washed with 3 x 2 mL of water and 2 mL of brine. The organic phase was shaken at 50 °C with 4 mL of 2.0 M acetic acid for 2 days. The aqueous phase was washed with 3 x 3 mL of ethyl acetate, made basic by addition of potassium hydroxide, saturated with sodium chloride and extracted with 3 x 2 mL of ethyl acetate. The organic phase was dried (MgSO₄) and concentrated under reduced pressure to give 78 mg (0.31 mmol, 79%) of the title compound as a colorless oil. LC-UV purity 95%. MS m/z 253 (M+1)⁺, calc. 253 (M+1)⁺.

Step 2: 2-[(2*R*)-2-Methylpiperazin-1-yl]-3-{2-[(2-[(2*S*)-1-methylpyrrolidin-2-yl]methoxy}pyridin-3-yl)oxy]ethoxy}pyrazine trifluoroacetate.

The procedure in Example 6, Step 2, was followed using 2-[(2-[(2*S*)-1-methylpyrrolidin-2-yl]methoxy}pyridin-3-yl)oxy]ethanol (from Step 1; 37 mg, 0.15 mmol) to give 39 mg (0.071 mmol, 71%) of the title compound as a brown oil. LC-UV purity 95%. HRMS m/z calcd for C₂₂H₃₂N₆O₃ (M)⁺ 428.2536, found 428.2523.

EXAMPLE 15

[2-({3-[2-({3-[(2*R*)-2-Methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)ethyl]amine, trifluoroacetate.

Step 1: *tert*-butyl (2-([3-(2-Hydroxyethoxy)pyridin-2-yl]oxy)ethyl)-carbamate.

A solution of 2-chloro-3-[2-(tetrahydro-2H-pyran-2-yloxy)ethoxy]pyridine (from Example 4; 100 mg, 0.39 mmol), 2-aminoethanol (35 μ l, 0.58 mmol) and 1.0 M potassium *tert*-butoxide in *tert*-butanol (0.8 mL, 0.80 mmol) in 4 mL of toluene was heated at 100 °C for 1 day. The organic phase was washed with 3 x 2 mL of 1.0 M NaOH and 1 mL of brine. Di-*tert*-butyl dicarbonate (94 mg, 0.43 mmol) was added and the reaction was shaken for 2 h and washed with 2 x 2 mL of NaOH followed by 2 x 2 mL of water. The organic phase was shaken with 4 mL of 2.0 M acetic acid for 1 week, washed with 4 x 2 mL of water, 2 x 2 mL of 1.0 M NaOH and 2 mL of brine, dried (MgSO₄) and concentrated under reduced pressure to give 53 mg (0.18 mmol, 46%) of the title compound as a colorless oil. LC-UV purity 90%. MS *m/z* 299 (M+1)⁺, calc. 299 (M+1)⁺.

Step 2: [2-([3-[2-([3-[(2*R*)-2-Methylpiperazin-1-yl]pyrazin-2-yl]oxy)ethoxy]pyridin-2-yl]oxy)ethyl]amine, trifluoroacetate.

To a solution of *tert*-butyl (2-([3-(2-hydroxyethoxy)pyridin-2-yl]oxy)ethyl)carbamate (from Step 1; 44 mg, 0.15 mmol) and 0.22 mL of 1.0 M potassium *tert*-butoxide in *tert*-butanol in 4 mL of dry methyl *tert*-butyl ether was *tert*-butyl (3*R*)-4-(3-chloropyrazin-2-yl)-3-methylpiperazine-1-carboxylate (from Example 5; 47 mg, 0.15 mmol) added and the mixture was shaken at room temperature for 2 days. The reaction mixture was quenched with 2 mL of water. The organic phase was washed with 3 x 2 mL of water and 2 mL of brine and concentrated under reduced pressure. The residue was purified with reversed phase chromatography. The purified product was concentrated, redissolved in 2 mL of chloroform and treated with 0.2 mL of trifluoroacetic acid for 2 h. The solvent was removed under reduced pressure to give 50 mg (0.10 mmol, 67%) of the title compound as a brown oil. LC-UV purity 100%. HRMS *m/z* calcd for C₁₈H₂₆N₆O₃ (M)⁺ 374.2066, found 374.2072.

EXAMPLE 16***N*-Methyl-2-([3-[2-([3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl]oxy)ethoxy]pyridin-2-yl]oxy)ethanamine, trifluoroacetate.****Step 1: 2-([2-[2-(Methylamino)ethoxy]pyridin-3-yl]oxy)ethanol.**

A solution of 2-chloro-3-[2-(tetrahydro-2H-pyran-2-yloxy)ethoxy]pyridine (from Example 4; 100 mg, 0.39 mmol), 2-(methylamino)ethanol (47 μ l, 0.58 mmol) and 1.0 M potassium *tert*-butoxide in *tert*-butanol (0.8 mL, 0.80 mmol) in 4 mL of toluene was heated at 100 °C for 1 day. The organic phase was washed with 3 x 2 mL of 1.0 M NaOH and 1 mL of brine. The

organic phase was shaken with 4 mL of 2.0 M acetic acid for 2 days. The aqueous phase was washed with 3 x 3 mL of ethyl acetate, made basic by addition of potassium hydroxide, saturated with sodium chloride and extracted with 3 x 2 mL of chloroform. The organic phase was dried (MgSO₄) and concentrated under reduced pressure to give 12 mg (0.056 mmol, 14%) of the title compound as a colorless oil. LC-UV purity 90%. MS *m/z* 213 (M+1)⁺, calc. 213 (M+1)⁺.

Step 2: *N*-Methyl-2-({3-[2-({3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)ethanamine, trifluoroacetate.

To a solution of 2-({2-[2-(methylamino)ethoxy]pyridin-3-yl}oxy)ethanol (from Step 1; 12 mg, 0.056 mmol) and 0.15 mL of 1.0 M potassium *tert*-butoxide in *tert*-butanol in 4 mL of dry methyl *tert*-butyl ether was *tert*-butyl (3*R*)-4-(3-chloropyrazin-2-yl)-3-methylpiperazine-1-carboxylate (from Example 5; 18 mg, 0.056 mmol) added and the mixture was stirred at room temperature for 3 days. The reaction mixture was quenched with 2 mL of 1.0 M NaOH. The organic phase was washed with 3 x 2 mL of 1.0 M NaOH and 1 mL of brine and concentrated under reduced pressure. The residue was purified by reversed phase chromatography. The purified product was concentrated, redissolved in 1 mL of chloroform and treated with 0.2 mL of trifluoroacetic acid for 1 hour. The solvent was removed under reduced pressure to give 32 mg (quantitative yield) of the title compound as a brown oil. LC-UV purity 100%. HRMS *m/z* calcd for C₁₉H₂₈N₆O₃ (M)⁺ 388.2223, found 388.2231.

EXAMPLE 17

2-{2-[2-[2-(Dimethylamino)ethoxy]pyridin-3-yl}oxy]ethoxy}-3-[(2*R*)-2,4-dimethylpiperazin-1-yl]pyrazine.

To a solution of 2-{2-[2-[2-(dimethylamino)ethoxy]pyridin-3-yl}oxy]ethoxy}-3-[(2*R*)-2-methylpiperazin-1-yl]pyrazine (from Example 1; 0.48 g, 1.19 mmol) in 1,2-dichloroethane (4 mL) was added sodium triacetoxyborohydride (1.3 g, 6.2 mmol) and 37% aqueous formaldehyde (0.072 g, 2.4 mmol), the slightly exothermic reaction was stirred at ambient temperature overnight. Water was added and the mixture was made basic (pH>13) by addition of 8 M NaOH. After being stirred for five minutes, the phases were separated and the aqueous phase was extracted twice with CHCl₃. The combined organic phases were dried (MgSO₄) and the solvent was removed under reduced pressure. The resulting oil was chromatographed on a column of silica (80 mm, i.d. = 30 mm) with CHCl₃/MeOH/NH₄OH (95:5:0.2; 100 mL,

followed by 90:10:0.2) as eluent to give 0.33 (67%) of the title compound as a colorless oil.
HRMS m/z calcd for $C_{21}H_{32}N_6O_3$ (M)⁺ 416.2536, found 416.2523.

EXAMPLE 18

5 **2-[2-(2-[2-(Dimethylamino)ethoxy]phenoxy)ethoxy]-3-[(2*R*)-2-methylpiperazin-1-yl]pyrazine.**

Step 1: *N*-{2-[2-(Benzyloxy)phenoxy]ethyl}-*N,N*-dimethylamine, hydrochloride.*

A mixture of 2-(benzyloxy)phenol (15.2 g, 75.9 mmol), *N*-(2-chloroethyl)-*N,N*-dimethylamine hydrochloride (16.4 g, 114 mmol) and potassium carbonate (55 g, 0.40 mol) in
10 dry acetone (200 mL) was heated at reflux. After 3 days (50% conversion according to HPLC), solids were filtered off, the solvent was removed under reduced pressure, and the remaining oil was taken up between $CHCl_3$ /0.5 M NaOH. The organic phase was washed once with water and dried. The organic phase (200 mL) was filtered through a plug of silica (60 mm x 60 mm), washed with $CHCl_3$ (100 mL) followed by $CHCl_3$ /MeOH (95:5; 500 mL).
15 Pure fractions were evaporated under reduced pressure to give 7.7 g of the free base of the title compound as a light brown oil. This material was dissolved in ether and HCl/ether was added to form the hydrochloride salt. This furnished 2.28 g (47%) of the title compound as white crystals: mp 144 °C. HRMS m/z calcd for $C_{17}H_{21}NO_2$ (M)⁺ 271.1572, found 271.1569.

*Reported in Bull. Soc. Chim. Fr. 1935, 1737-1741.

20 **Step 2: 2-[2-(Dimethylamino)ethoxy]phenol.***

To a solution of *N*-{2-[2-(benzyloxy)phenoxy]ethyl}-*N,N*-dimethylamine (from Step 1; 7.60 g, 28.0 mmol) in MeOH (80 mL) was added 10% Pd/C (0.8 g) and the mixture was
hydrogenated at 70 psi and room temperature for 2 h. The reaction mixture was filtered
25 through a pad of Celite[®] and silica. The solvent was then removed under reduced pressure to give 5.43 g (quantitative yield) of the title compound as off-white crystals: mp 220 °C. HRMS m/z calcd for $C_{10}H_{15}NO_2$ (M)⁺ 181.1103 Found 181.1105. *The corresponding hydrochloride salt has been reported in Bull. Soc. Chim. Fr. 1935, 1737-1741.

30 **Step 3: 2-{2-[2-(Dimethylamino)ethoxy]phenoxy}ethanol.**

To dry DMF (50 mL) was added 2-[2-(dimethylamino)ethoxy]phenol (from Step 1; 5.4 g, 28.0 mmol), ethylene carbonate (3.20 g, 36.4 mmol) and potassium carbonate (3.9 g, 28 mmol) and the mixture was heated at 155 °C for one hour 30 minutes. The solvent from the filtered solution was evaporated under reduced pressure and the resulting residue was

dissolved in CHCl_3 (50 mL) and filtered through a plug of silica (50 mm x 50 mm) using CHCl_3 (50 mL) followed by $\text{CHCl}_3/\text{MeOH}$ (95:5) as eluents. Solvents from the pure fractions were removed under reduced pressure to give 4.8 g (76%) of the title compound as a light brown oil. HRMS m/z calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_3$ (M)⁺ 225.1365, found 225.1363.

5

Step 4: 2-[2-(2-[2-(Dimethylamino)ethoxy]phenoxy)ethoxy]-3-[(2R)-2-methylpiperazin-1-yl]pyrazine.

To a solution of 2-{2-[2-(dimethylamino)ethoxy]phenoxy} ethanol (from Step 3; 0.82 g, 3.6 mmol) in dry DMF (25 mL) was added potassium *tert*-butoxide (0.59 g, 5.3 mmol) and the mixture was stirred at room temperature for 10 minutes. To the mixture was added 2-chloro-3-[(2R)-2-methylpiperazin-1-yl]pyrazine* (0.70 g, 3.3 mmol) in DMF (5 mL) in one portion and the reaction mixture was stirred at 55 °C for 2 h. A small spoon of silica was added, the solvent was filtered off and the solvent was evaporated under reduced pressure. The crude product was purified on a column of silica (100 mm, i.d. = 30 mm) with $\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH}$ (95:5:0.2; 100 mL, followed by 90:10:0.2) as eluent to give 0.80 g (60%) of the title compound as a light brown oil. HRMS m/z calcd for $\text{C}_{21}\text{H}_{31}\text{N}_5\text{O}_3$ (M)⁺ 401.2427, found 401.2414. *Reported in WO 00/76984, Example 192, Step 2.

EXAMPLE 19

2-[2-[(2-{[2-(Dimethylamino)ethoxy]methyl}pyridin-3-yl)oxy]ethoxy]-3-[(2R)-2-methylpiperazin-1-yl]pyrazine.

Step 1: {3-[2-(Tetrahydro-2H-pyran-2-yloxy)ethoxy]pyridin-2-yl}methanol.

A suspension of 85% pure 2-(hydroxymethyl)pyridin-3-ol hydrochloride (24.9 g, 130 mmol) and potassium carbonate (60 g, 434 mmol) in acetonitrile (200 mL) was heated at reflux for 15 minutes after which 2-(2-bromoethoxy)tetrahydro-2H-pyran (32.9 g, 160 mmol) was added in one portion and the heating was continued overnight. Solids were filtered off and the solvent was removed under reduced pressure and the resulting oil was chromatographed on a column of silica (100 mm, i.d. = 60 mm) with CHCl_3 as eluent followed by $\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH}$ (95:5:0.2) to give 28.4 g (93%) of the title compound as a light brown oil. HRMS m/z calcd for $\text{C}_{13}\text{H}_{19}\text{NO}_4$ (M)⁺ 253.1314, found 253.1326.

Step 2: {3-[2-(Tetrahydro-2H-pyran-2-yloxy)ethoxy]pyridin-2-yl}methyl methanesulfonate.

To an ice cold solution of {3-[2-(tetrahydro-2H-pyran-2-yloxy)ethoxy]pyridin-2-yl}methanol (from Step 1; 3.39 g, 13.4 mmol) and triethylamine (1.95 g, 19.3 mmol) in dry DCM (25 mL) under an atmosphere of N₂ was a solution of methanesulfonic anhydride in DCM (10 mL) added during five minutes. The mixture was stirred at 0 °C for one hour followed by one hour at room temperature. Water (10 mL) was added and the phases were separated. The organic phase was washed once with brine, dried (MgSO₄) and the solvent was removed under reduced pressure to give 4.50 g (quantitative yield) of a slightly reddish oil that darkened upon standing. The crude product was used directly in the next step without further purification.

Step 3: N-(2-{[3-(2-(Tetrahydro-2H-pyran-2-yloxy)ethoxy)pyridin-2-yl]methoxy}ethyl)-N,N-dimethylamine.

To a solution of 2-(N,N-dimethylamino)ethanol (0.84 g, 9.4 mmol) in dry dioxane (30 mL) was added potassium *tert*-butoxide (0.92 g, 8.2 mmol) and the mixture was stirred at room temperature for 20 minutes after which time a solution of {3-[2-(tetrahydro-2H-pyran-2-yloxy)ethoxy]pyridin-2-yl}methyl methanesulfonate (from Step 2; 2.1 g, 6.3 mmol) in dioxane (10 mL) was added. The initially slightly exothermic reaction was stirred at ambient temperature overnight. The solvent from the reaction mixture was evaporated under reduced pressure and the resulting oil was taken up between CHCl₃/water. The aqueous phase was extracted once with CHCl₃ and the combined organic phases were dried (MgSO₄) and the solvent was again evaporated. The resulting oil was chromatographed on a column of silica (100 mm, i.d. = 30 mm) with initially CHCl₃ 100% (100 mL) followed by CHCl₃/MeOH/NH₄OH (95:5:0.2; 100 mL, and thereafter 90:10:0.2) to give 0.74 g (36%) of the title compound as a brown oil. HRMS *m/z* calcd for C₁₇H₂₈N₂O₄ (M)⁺ 324.2049, found 324.2042.

Step 4: 2-[(2-{[3-(2-(Tetrahydro-2H-pyran-2-yloxy)ethoxy)pyridin-3-yl]oxy}ethyl)-N,N-dimethylamine]

A solution of N-(2-{[3-(2-(tetrahydro-2H-pyran-2-yloxy)ethoxy)pyridin-2-yl]methoxy}ethyl)-N,N-dimethylamine (from Step 3; 0.69 g, 2.13 mmol) in 2 M HOAc (20 mL) was stirred at 50 °C for two days. The reaction mixture was washed with CHCl₃ (x 3), saturated with sodium chloride, made basic by addition of 8 M NaOH, and extracted with CHCl₃ (x 3). The solvent

from the combined organic phases was removed under reduced pressure to give 0.47 g (92%) of the title compound as a light brown oil. HRMS m/z calcd for $C_{12}H_{20}N_2O_3$ (M)⁺ 240.1474, found 240.1476.

5 **Step 5: 2-{2-[(2-{[2-(Dimethylamino)ethoxy]methyl}pyridin-3-yl)oxy]ethoxy}-3-[(2R)-2-methylpiperazin-1-yl]pyrazine.**

The procedure in Example 18, Step 4, was followed starting from 2-chloro-3-[(2R)-2-methylpiperazin-1-yl]pyrazine* (0.27 g, 1.28 mmol) and 2-[(2-{[2-(dimethylamino)ethoxy]methyl}pyridin-3-yl)oxy]ethanol (from Step 4; 0.28 g, 1.16 mmol).

10 The crude product was purified on a column of silica (100 mm, i.d. = 30 mm) with $CHCl_3/MeOH/NH_4OH$ (80:20:0.5; 200 mL followed by 60:40:1; 100 mL and thereafter 50:50:1) as eluent to give 0.25 g (51%) of the title compound as a light brown oil. HRMS m/z calcd for $C_{21}H_{32}N_6O_3$ (M)⁺ 417.2536, found 417.2541. *Reported in WO 00/76984, Example 192, Step 2.

15

EXAMPLE 20

2-{2-[(2-{[2-(1Z)-3-(Dimethylamino)prop-1-enyl]pyridin-3-yl)oxy]ethoxy}-3-[(2R)-2-methylpiperazin-1-yl]pyrazine.

Step 1: 3-[2-(Tetrahydro-2H-pyran-2-yloxy)ethoxy]pyridine-2-carbaldehyde.

20 To a three-necked round flask containing dry DCM (500 mL) cooled down to $-78^\circ C$ under an atmosphere of N_2 was added oxalyl chloride (20.0 mL, 157 mmol) followed by a careful dropwise addition of DMSO (24.5 g, 315 mmol). To the cold reaction mixture was {3-[2-(tetrahydro-2H-pyran-2-yloxy)ethoxy]pyridin-2-yl}methanol (from Example 19, Step 1; 21.0 g, 82.9 mmol) in DCM (25 mL) carefully added, the temperature never exceeded
25 $-65^\circ C$. After the addition, the reaction mixture was stirred at $-78^\circ C$ for one hour after which time TEA (50.2 g, 497 mmol) was added and the mixture was stirred another 30 minutes at ambient temperature. To the mixture was added ice water (400 mL) and the organic phase was washed H_2O , brine, dried ($MgSO_4$), the brown organic phase was filtered through a pad (60 mm x 40 mm) of silica and finally the solvent was removed under reduced pressure to
30 give a brown oil. The hydrated aldehyde was dissolved in toluene (150 mL) and heated for 3 h under Dean-Stark conditions to give 19.9 g (95%) of the title compound as a black oil. HRMS m/z calcd for $C_{13}H_{17}NO_4$ (M)⁺ 251.1158, found 251.1153.

Step 2: *N,N*-dimethyl-*N*-((2*Z*)-3-{3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]pyridin-2-yl}prop-2-enyl)amine.

To a suspension of [2-(dimethylamino)ethyl](triphenyl)phosphonium bromide (32.1 g, 77.4 mmol) in dry THF (150 mL) was added a solution of potassium *tert*-butoxide (9.4 g, 83.7 mmol) in dry *t*-BuOH (100 mL). The suspension was sonicated for 15 minutes whereafter a solution of 3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]pyridine-2-carbaldehyde (from Step 1; 18.3 g, 72.8 mmol) in THF (30 mL) was added to the yellow suspension and stirred at room temperature for one hour and then for a further hour at 60 °C. The solvent was removed under reduced pressure and the residue was mixed with water (0.8 L) and the pH was adjusted to 3-4 with HOAc (~ 10 mL) and then extracted twice with CHCl₃. The aqueous phase was made basic and extracted with CHCl₃ (x 3), the combined organic phases were dried (MgSO₄) and the solvent was removed under reduced pressure. The crude product, consisting of the *cis* and *trans** isomers were separated with preparative HPLC on an YMC ODS-AQ column (30 x 250 mm) with different gradients of 0.1% TFA in water/CH₃CN. The *cis* isomer was isolated as a light yellow oil (2.33 g, 10%). HRMS *m/z* calcd for C₁₇H₂₆N₂O₃ (M)⁺ 306.1943, found 306.1942. *The corresponding *trans* isomer is described in Example 21, Step 1.

Step 3: 2-({2-[(1*Z*)-3-(Dimethylamino)prop-1-enyl]pyridin-3-yl}oxy)ethanol.

The procedure in Example 19, Step 4, was followed using *N,N*-dimethyl-*N*-((2*Z*)-3-{3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]pyridin-2-yl}prop-2-enyl)amine (from Step 2; 1.3 g, 4.2 mmol) to give 0.86 g (91%) of the title compound as a colorless oil that crystallized upon standing: mp 71°C. HRMS *m/z* calcd for C₁₂H₁₈N₂O₂ (M)⁺ 222.1368, found 222.1363.

Step 4: 2-{2-[(1*Z*)-3-(Dimethylamino)prop-1-enyl]pyridin-3-yl}oxyethoxy}-3-[(2*R*)-2-methylpiperazin-1-yl]pyrazine.

The procedure in Example 18, Step 4, was followed starting from 2-chloro-3-[(2*R*)-2-methylpiperazin-1-yl]pyrazine* (0.23 g, 1.0 mmol) and 2-({2-[(1*Z*)-3-(dimethylamino)prop-1-enyl]pyridin-3-yl}oxy)ethanol (from Step 3; 0.24 g, 1.1 mmol). The crude product was purified on a column of silica (100 mm, i.d. = 30 mm) with CHCl₃/MeOH/NH₄OH (80:20:0.5; 200 mL, followed by 60:40:1) as eluent to give 0.050 g (12%) of the title compound as a light brown oil. HRMS *m/z* calcd for C₂₁H₃₀N₆O₂ (M)⁺ 398.2430, found 398.2438. *Reported in WO 00/76984, Example 192, Step 2.

EXAMPLE 21

2-{2-[[2-[(1*E*)-3-(Dimethylamino)prop-1-enyl]pyridin-3-yl]oxy]ethoxy}-3-[(2*R*)-2-methylpiperazin-1-yl]pyrazine.

Step 1: *N,N*-dimethyl-*N*-((2*E*)-3-{3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]pyridin-2-yl}prop-2-enyl)amine.

- 5 The title *trans* isomer compound was isolated as a light yellow oil (1.2 g, 5.5%) from the reaction performed in Example 20, Step 2. HRMS *m/z* calcd for C₁₇H₂₆N₂O₃ (M)⁺ 306.1943, found 306.1934.

Step 2: 2-({2-[(1*E*)-3-(Dimethylamino)prop-1-enyl]pyridin-3-yl}oxy)ethanol.

- 10 The procedure in Example 19, Step 4, using *N,N*-dimethyl-*N*-((2*E*)-3-{3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]pyridin-2-yl}prop-2-enyl)amine (from Step 1; 1.0 g, 3.3 mmol) was followed to give 0.83 g (quantitative yield) of the title compound as a light brown oil. HRMS *m/z* calcd for C₁₂H₁₈N₂O₂ (M)⁺ 222.1368, found 222.1364.

- 15 Step 3: 2-{2-[[2-[(1*E*)-3-(Dimethylamino)prop-1-enyl]pyridin-3-yl]oxy]ethoxy}-3-[(2*R*)-2-methylpiperazin-1-yl]pyrazine.

- The procedure in Example 18, Step 4, was followed starting from 2-chloro-3-[(2*R*)-2-methylpiperazin-1-yl]pyrazine* (0.30 g, 1.4 mmol) and 2-({2-[(1*E*)-3-(dimethylamino)prop-1-enyl]pyridin-3-yl}oxy)ethanol (from Step 2; 0.32 g, 1.5 mmol). The crude product was
20 purified on a column of silica (100 mm, i.d. = 30 mm) with CHCl₃/MeOH/NH₄OH (80:20:0.5; 200 mL, followed by 60:40:1) as eluent to give 0.030 g (5.5%) of the title compound as a light brown oil. HRMS *m/z* calcd for C₂₁H₃₀N₆O₂ (M)⁺ 398.2430, found 398.2433. *Reported in WO 00/76984, Example 192, Step 2.

25 EXAMPLE 22

2-{2-[[2-3-(Dimethylamino)propyl]pyridin-3-yl]oxy]ethoxy}-3-[(2*R*)-2-methylpiperazin-1-yl]pyrazine.

Step 1: 2-({2-3-(Dimethylamino)propyl}pyridin-3-yl)oxy)ethanol.

- To a mixture of the *cis* and *trans* isomers *N,N*-dimethyl-*N*-((2*E* and 2*Z*)-3-{3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]pyridin-2-yl}prop-2-enyl)amine (from Example 20, Step 2; 3.1 g, 10.1 mmol) in MeOH (50 mL) was added 10% Pd/C (0.30 g) and the mixture was
30 hydrogenated in a Parr apparatus at room temperature at 70 psi H₂ overnight. The solvent from the filtered solution was removed under reduced pressure and the tetrahydropyranyl protecting group was removed using the procedure described in Example 19, Step 4, to yield

1.29 g (57%) of the title compound as a brown oil. HRMS m/z calcd for $C_{12}H_{20}N_2O_2$ (M)⁺ 224.1525, found 224.1521.

Step 2: 2-{2-[(2-{3-(Dimethylamino)propyl}pyridin-3-yl)oxy]ethoxy}-3-[(2*R*)-2-methylpiperazin-1-yl]pyrazine.

The procedure in Example 18, Step 4, starting from 2-chloro-3-[(2*R*)-2-methylpiperazin-1-yl]pyrazine* (0.48 g, 2.28 mmol) and 2-[(2-{3-(dimethylamino)propyl}pyridin-3-yl)oxy]ethanol (from Step 1; 0.46 g, 2.07 mmol) was followed. The crude product was purified on a column of silica (100 mm, i.d. = 30 mm) with $CHCl_3/MeOH/NH_4OH$ (80:20:0.5; 200 mL, followed by 60:40:1) as eluent to give 0.48 g (58%) of the title compound as a colorless oil. HRMS m/z calcd for $C_{21}H_{32}N_6O_2$ (M)⁺ 400.2587, found 400.2571. *Reported in WO 00/76984, Example 192, Step 2.

EXAMPLE 23

15 {2-[2-[(3-[2-[(2*R*)-2-Methylpiperazin-1-yl]pyrazin-2-yl)oxy]ethoxy]pyridin-2-yl)oxy]ethoxy]ethyl}amine, bis(trifluoroacetate).

Step 1: *tert*-Butyl {2-[2-[(3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]pyridin-2-yl)oxy]ethoxy]ethyl}carbamate.

2-(2-Aminoethoxy)ethanol (0.45 g, 4.3 mmol) and 2-chloro-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]pyridine (from Example 4; 1.0 g, 3.9 mmol) was added to a solution of potassium *tert*-butoxide (0.52 g, 4.7 mmol) in dry DMSO (4 mL). The mixture was heated at 90 °C for five minutes. After this time, the reaction mixture was cooled to ambient temperature. Di-*tert*-butyl dicarbonate (1.1 g, 5.0 mmol) was added and the resulting mixture was stirred for one hour at room temperature. Pyridine (0.3 mL) was added and the mixture left at room temperature over night. The reaction mixture was diluted with water (10 mL) and extracted with $CHCl_3$ (x 3), the combined organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The remaining oil was chromatographed on a column of silica with DCM/MeOH (98:2) as eluent to give 0.76 g (46%) of the title compound as a colorless oil. LC-UV purity: system (A) 96%. HRMS m/z calcd for $C_{21}H_{34}N_2O_7$ (M)⁺ 426.2366, found 426.2355.

Step 2: *tert*-Butyl (3*R*)-4-[3-(2-{2-[2-[(*tert*-butoxycarbonyl)amino]ethoxy}-ethoxy]pyridin-3-yl)oxy]ethoxy]pyrazin-2-yl]-3-methylpiperazine-1-carboxylate.

tert-Butyl {2-[2-({3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]pyridin-2-yl}oxy)ethoxy]ethyl} carbamate (from Step 1; 0.74 g, 1.7 mmol) was suspended in 2 M HOAc (5 mL) and acetonitrile (1 mL) and heated at 50 °C for two days. The solution was neutralized with concentrated aqueous ammonia. Brine was added (3 mL) and the mixture was extracted with CHCl₃ (x 3). The combined organic phases were dried (MgSO₄) and the solvent was removed under reduced pressure. The remaining oil was dissolved in dry DMSO (10 mL), potassium *tert*-butoxide (0.36 g, 3.2 mmol) was added followed by *tert*-butyl (3*R*)-4-(3-chloropyrazin-2-yl)-3-methylpiperazine-1-carboxylate (from Example 5; 0.59 g, 1.9 mmol) and the mixture was heated at 50 °C for 20 minutes. The reaction mixture was diluted with water/brine (90:10) and extracted with CHCl₃ (x 3). The combined organic phases were dried (MgSO₄), the solvent was removed under reduced pressure and the remaining oil was chromatographed on a column of silica with hexane/EtOAc (70:30) as eluent to give 0.43 g (40%) of the title compound as a colorless oil. LC-UV purity: system (A) 100%. HRMS *m/z* calcd for C₃₀H₄₆N₆O₈ (M)⁺ 618.3377, found 618.3381.

Step 3: {2-[2-({3-[2-({3-[(2*R*)-2-Methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)ethoxy]ethyl}amine, bis(trifluoroacetate).

A solution of *tert*-butyl (3*R*)-4-[3-(2-{[2-(2-{[*tert*-butoxycarbonyl)amino]ethoxy}ethoxy)pyridin-3-yl]oxy}ethoxy)pyrazin-2-yl]-3-methylpiperazine-1-carboxylate (from Step 2; 0.405 g, 0.655 mmol) in DCM/TFA (1:1; 4 mL) was stirred at room temperature over night. The solvent was removed under reduced pressure and the remaining oil was dried (1 mm Hg, 40 °C) over night to give 0.424 g (100%) of the title compound as a brown oil. LC-UV purity: system (A) 99%, (B) 98%. HRMS *m/z* calcd for C₂₀H₃₀N₆O₄ (M)⁺ 418.2329, found 418.2337.

EXAMPLE 24

[6-({3-[2-({3-[(2*R*)-2-Methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)hexyl]amine, trifluoroacetate.

Step 1: (6-{3-[2-(Tetrahydro-2*H*-pyran-2-yloxy)-ethoxy]-pyridin-2-yloxy}-hexyl)-carbamic acid *tert*-butyl ester.

The title compound was prepared according to the procedure in Example 23, Step 1, starting from 2-chloro-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]pyridine (from Example 4; 1.0 g, 3.9 mmol) and 6-amino-1-hexanol (0.50 g, 4.3 mmol). Yield 1.0 g (58 %).

Step 2: [6-({3-[2-({3-[(2*R*)-2-Methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)hexyl]amine, trifluoroacetate.

The title compound was prepared starting from (6-{3-[2-(tetrahydro-2*H*-pyran-2-yloxy)-ethoxy]-pyridin-2-yloxy}-hexyl)-carbamic acid *tert*-butyl ester (from Step 1; 1.0 g, 2.3 mmol)

- 5 by first removing the tetrahydropyranyl protecting group followed by subsequent reaction with *tert*-butyl (3*R*)-4-(3-chloropyrazin-2-yl)-3-methylpiperazine-1-carboxylate (from Example 5; 0.73 g, 2.3 mmol) according to the procedure in Example 23, Step 2, followed by *N*-Boc deprotection according to the procedure in Example 23, Step 3. Yield 62 mg (6 %).

LC-UV purity: system (A) 97%, (B) 97%. HRMS *m/z* calcd for C₂₂H₃₄N₆O₃ (M)⁺ 430.2692,
10 found 430.2676.

EXAMPLE 25

[5-({3-[2-({3-[(2*R*)-2-Methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)pentyl]amine, bis(trifluoroacetate).

- 15 The title compound was prepared analogously to Example 24 by substituting 5-amino-1-pentanol (1.76 g, 17.0 mmol) for 6-amino-1-hexanol. Yield 0.126 g (3%). LC-UV purity: system (A) 98%, (B) 97%. HRMS *m/z* calcd for C₂₁H₃₂N₆O₃ (M)⁺ 416.2536, found 416.2547.

20 EXAMPLE 26

5-({3-[2-({3-[(2*R*)-2,4-Dimethylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)-*N,N*-dimethylpentan-1-amine.

- [5-({3-[2-({3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)pentyl]amine bis(trifluoroacetate) (from Example 25; 0.17 g, 0.26 mmol), 1,2-
25 dichloroethane (5 mL), 37% aqueous formaldehyde (0.13 g, 1.6 mmol) and sodium triacetoxyborohydride (0.66 g, 3.1 mmol) was mixed and the mixture was stirred at 50 °C over night. The reaction mixture was quenched with a few drops of 8 M NaOH, diluted with water and extracted twice with CHCl₃. The combined organic phases were dried (Hydromatrix) and evaporated under reduced pressure. The crude oil was purified with a
30 preparative LC-MS system (B) to give 36 mg (30%) of the target compound as a light brown oil. LC-UV purity: system (A) 100%, (B) 100%. HRMS *m/z* calcd for C₂₄H₃₈N₆O₃ (M)⁺ 458.3005, found 458.3013.

EXAMPLE 27

2-[(2*R*)-2-Methylpiperazin-1-yl]-3-(2-{[2-(2-piperazin-1-ylethoxy)pyridin-3-yl]oxy}ethoxy)pyrazine, trifluoroacetate.

Step 1: 4-{2-[3-(2-Hydroxy-ethoxy)-pyridin-2-yloxy]-ethyl}-piperazine-1-carboxylic acid *tert*-butyl ester.

- 5 The title compound was prepared starting from 2-chloro-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]pyridine (from Example 4; 0.67 g, 2.6 mmol) and *tert*-butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (0.66 g, 2.9 mmol) according to the procedure in Example 23, Step 1, followed by removing the tetrahydropyranyl protecting group according to the procedure given in Example 23, Step 2. Yield 0.36 g (38 %). MS (ESI+) for
- 10 $C_{18}H_{29}N_3O_5$ m/z 368.0 (M+H)⁺.

Step 2: 2-[(2*R*)-2-Methylpiperazin-1-yl]-3-(2-{[2-(2-piperazin-1-ylethoxy)pyridin-3-yl]oxy}ethoxy)pyrazine, trifluoroacetate.

- The title compound was prepared by reaction of 4-{2-[3-(2-hydroxy-ethoxy)-pyridin-2-yloxy]-ethyl}-piperazine-1-carboxylic acid *tert*-butyl ester (from Step 1; 0.367 g, 1.00 mmol)
- 15 with *tert*-butyl (3*R*)-4-(3-chloropyrazin-2-yl)-3-methylpiperazine-1-carboxylate (from Example 5; 0.313 g, 1.00 mmol) according to the procedure in Example 23, Step 2, followed by removal of the *N*-Boc protecting group according to the procedure in Example 23, Step 3. Yield 12 mg (2 %). LC-UV purity: system (A) 80%, (B) 85%. HRMS m/z calcd for
- 20 $C_{22}H_{33}N_7O_3$ (M)⁺ 443.2645 found 443.2646.

PREPARATION OF A PHARMACEUTICAL COMPOSITION

EXAMPLE: Preparation of tablets

25	<u>Ingredients</u>	<u>mg/tablet</u>
	1. Active compound of Formula (I)	10.0
	2. Cellulose, microcrystalline	57.0
	3. Calcium hydrogen phosphate	15.0
	4. Sodium starch glycolate	5.0
30	5. Silicon dioxide, colloidal	0.25
	6. Magnesium stearate	0.75

The active ingredient 1 is mixed with ingredients 2, 3, 4 and 5 for about 10 minutes. The magnesium stearate is then added, and the resultant mixture is mixed for about 5 minutes and compressed into tablet form with or without film-coating.

5 Pharmacological tests

The ability of a compound of the invention to bind or act at specific 5-HT receptor subtypes can be determined using *in vitro* and *in vivo* assays known in the art. The biological activity of compounds prepared in the Examples was tested using different tests.

10 Affinity assays

The receptor affinity of compounds in the Examples was determined in competition experiments, where the ability of each compound in serial dilution to displace ^3H -labelled 5-HT, bound to membranes prepared from a transfected HEK293 cell line stably expressing the human 5-HT_{2C} receptor protein, was monitored by Scintillation Proximity Assay technology.

15 Non-specific binding was defined using 5 μM mianserin. Results obtained for exemplary compounds of the invention are illustrated below.

The binding affinities of the compounds for the human 5-HT_{2A} and 5-HT_{2B} receptors in CHO cell lines were determined using ^3H -labelled lysergic acid diethyl amide (LSD) and 5-HT, respectively, as radioligands. The binding affinities of the compounds for the human 5-HT_{1A} and 5-HT_{1B} receptors in CHO cell lines were determined similarly using ^3H -labelled 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) and 5-HT, respectively, as radioligands.

In vitro functional assays

25 The agonist efficacy at the 5-HT_{2C} receptor of the compounds in the Examples was determined by the ability of each compound to mobilise intracellular calcium in transfected HEK293 cells, stably expressing the human 5-HT_{2C} receptor protein, using the calcium-chelating fluorescent dye FLUO-3 (Sigma, St. Louis, MO, U.S.A.).

The ability of the compounds to mobilise intracellular calcium at the 5HT_{2A} and 5-HT_{2B} receptors was determined similarly using CHO cells expressing the human 5-HT_{2A} or human 5-HT_{2B} receptors.

The maximum functional responses of the compounds, at 1 μ M, at the 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors are expressed relative to the maximum response of 5-HT (serotonin) at a concentration of 1 μ M.

5 EXAMPLE 28

Test compound was Example 1. Affinity (K_i) was determined using three separate weightings, analyzed on two different occasions, except for the 5-HT_{2C} values which are based on three separate weighings, analyzed on three different occasions (12 individual K_i-values). EC₅₀ (the concentration at which a half-maximal effect occurs) and % efficacy are
10 from 2-5 determinations.

	5-HT _{2A}	5-HT _{2B}	5-HT _{2C}	5-HT _{1A}	5-HT _{1B}
K _i (nM)	> 1 000	> 1000	12	800	> 1000
EC ₅₀ (nM)	1200	1940	4.2		
Efficacy	14	16	117		

EXAMPLE 29

Test compound was Example 2. Affinity (K_i) was determined using three separate weightings. EC₅₀ and % efficacy are from 3-4 determinations.

	5-HT _{2A}	5-HT _{2B}	5-HT _{2C}	5-HT _{1A}	5-HT _{1B}
K_i (nM)	> 1.000	> 1000	10	380	200
EC₅₀ (nM)	260	900	3.9		
Efficacy	40	33	111		

5

The receptor affinity of some compounds as described in WO 00/76984 are given below.

Example 177 of WO 00/76984

	5-HT _{2A}	5-HT _{2B}	5-HT _{2C}	5-HT _{1A}	5-HT _{1B}
K_i (nM)	177	530	7	517	1548
Efficacy	34	28	95		

10

Example 193 of WO 00/76984

	5-HT _{2A}	5-HT _{2B}	5-HT _{2C}	5-HT _{1A}	5-HT _{1B}
K_i (nM)	498	267	10	155	507
Efficacy	47	8	112		

Example 194 of WO 00/76984

15

	5-HT _{2A}	5-HT _{2B}	5-HT _{2C}	5-HT _{1A}	5-HT _{1B}
K_i (nM)	234	334	7	567	> 1000
Efficacy	64	21	98		

As is evident from comparisons above, the 5-HT_{2C} receptor selectivity (i.e. the K_i for 5-HT_{2C} compared to 5-HT_{2A} and 5-HT_{2B}) of the compounds according to the present invention is unexpectedly high compared to the compounds according to WO 00/76984.

20

The receptor affinity of some compounds as described in WO 02/40457 are given below.

Example 2 of WO 02/40457

	5-HT _{2A}	5-HT _{2B}	5-HT _{2C}	5-HT _{1A}	5-HT _{1B}
Ki (nM)	787	107	4	28	51
Efficacy	48	27	74		

Example 5 of WO 02/40457

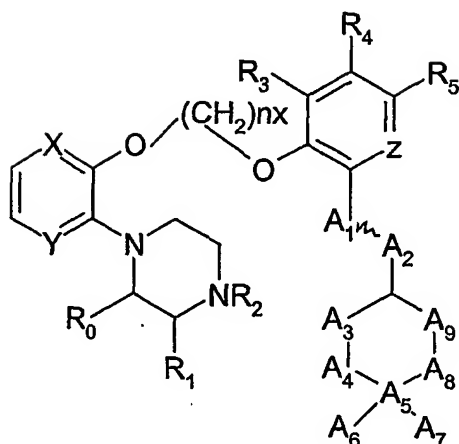
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	5-HT _{2A}	5-HT _{2B}	5-HT _{2C}	5-HT _{1A}	5-HT _{1B}
Ki (nM)	> 1000	89	2.4	29	19
Efficacy	41	27	97		

As is evident from comparisons above, the 5-HT_{2C} receptor selectivity (i.e. the Ki for 5-HT_{2C} compared to 5-HT_{2B}, 5-HT_{1A} and 5-HT_{1B}) of the compounds according to the present invention is unexpectedly high compared to the compounds according to WO

10 02/40457.

1. A compound of Formula (I):



Formula (I)

wherein

nx is 2-4, preferably 2;

R₀ and R₁ are each independently H or CH₃;

R₂ is H, C₁-C₄-alkyl, 2-hydroxyethyl, 2-cyanoethyl or tetrahydropyran-2-yl, C₁-C₄-acyl or C₁-C₄-alkoxycarbonyl;

R₃-R₅ are each independently H, halogen, methyl or methoxy, provided that at least one of R₃-R₅ is hydrogen;

X, Y, and Z are each independently CH or N;

A₁ is O, CH or CH₂;

A₂ is O, CH or (CH₂)_{n2}, wherein n₂ is an integer 0-2;

the bond between A₁ and A₂ is a single or double bond;

A₃ is (CH₂)_{n3}, wherein n₃ an integer 0-10, preferably 0-7, more preferably 0-5;

A₄ is (CMe₂)_{n4}, wherein n₄ is an integer 0-1;

A₅ is N or O;

A₆ and A₇ are each independently H, C₁-C₄-alkyl, amino-C₂-C₄-alkyl, N,N-di-C₁-C₄-alkylamino-C₂-C₄-alkyl, C₃-C₆-cycloalkyl or form together with A₅ a saturated heterocyclic ring;

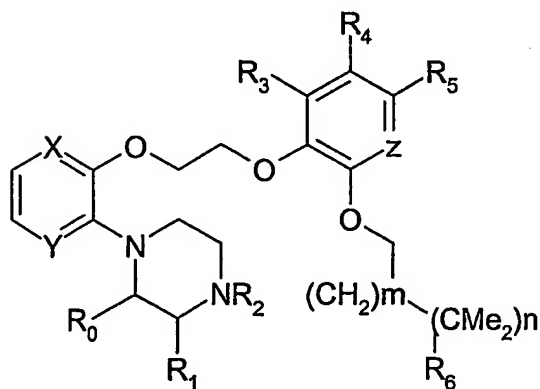
A₈ is (CH₂)_{n8}, wherein n₈ is an integer 0-2;

A₉ is H or CH₂;

or pharmaceutically acceptable salts, solvates, hydrates, geometrical isomers, tautomers, optical isomers, N-oxides and prodrug forms thereof.

- 5 2. The compound according to claim 1, wherein R₀ is methyl.
3. The compound according to any one of claims 1 to 2, wherein the carbon atom, to which the said methyl group R₀ is attached, is in the (*R*)-configuration.
- 10 4. The compound according to claim 1, wherein R₀ is hydrogen.
5. The compound according to any one of claims 1 to 4, wherein R₁ is hydrogen.
6. The compound according to any one of claims 1 to 5, wherein X and Y both are nitrogen.
- 15 7. The compound according to any one of claims 1 to 6, wherein R₂ is H or methyl.
8. The compound according to any one of claims 1 to 7, wherein all of R₃-R₅ are H.
- 20 9. The compound according to any one of claims 1 to 8, wherein A₆ and A₇ are each independently H, methyl, isopropyl, 2-ethylamine or form together a pyrrolidine or piperazine ring.
10. The compound according to any one of claims 1 to 9, which has the Formula (Ia):

25



Formula (Ia)

wherein:

R_0 - R_5 , X, Y, and Z are as defined in any one of claims 1 to 8, preferably wherein Z is N,

5 m is an integer 0-10, preferably 0-7, more preferably 0-5,

n is an integer 0 or 1, wherein the sum of m + n is preferably at least 1,

R_6 is NR_7R_8 or OR_9 , wherein

R_7 and R_8 are each independently H or straight or branched C_1 - C_4 -alkyl;

or R_7 and R_8 form together with the nitrogen atom to which they are attached a

10 saturated heterocyclic ring;

R_9 is amino- C_2 - C_4 -alkyl or N,N-di- C_1 - C_4 -alkylamino- C_2 - C_4 -alkyl.

11. The compound according to claim 10, wherein R_7 and R_8 are selected from H, methyl, isopropyl, or form together with the nitrogen atom to which they are attached a
15 pyrrolidine or piperazine ring.

12. The compound according to any one of claims 10 or 11, wherein R_9 is 2-aminoethyl.

20 13. The compound according to any one of claims 10-12, which compound is:

N,N-Dimethyl-(2-(3-[2-(2-(*R*)-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrazinyl-3'-yloxy)-ethoxy]-pyridin-2-yloxy)-ethyl)-amine;

N,N-Diisopropyl-(2-(3-[2-(2-(*R*)-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrazinyl-3'-yloxy)-ethoxy]-pyridin-2-yloxy)-ethyl)-amine;

25 *N,N*-Dimethyl-2-[(3-{2-[(3-piperazin-1-ylpyrazin-2-yl)oxy]ethoxy}pyridin-2-yl)oxy]ethanamine;

2-[(2*R*)-2-Methylpiperazin-1-yl]-3-(2-{[2-(2-pyrrolidin-1-ylethoxy)pyridin-3-yl]oxy}ethoxy)pyrazine,;

N,N-Dimethyl-4-[(3-[2-[(3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl)oxy]ethoxy]pyridin-2-yl)oxy]butan-1-amine;

30 *N*-Methyl-*N*-[2-[(3-[2-[(3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl)oxy]ethoxy]pyridin-2-yl)oxy]ethyl]propan-2-amine;

N,N-Dimethyl-3-({3-[2-({3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)propan-1-amine;

N,N,2-Trimethyl-1-({3-[2-({3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)propan-2-amine;

5 [2-({3-[2-({3-[(2*R*)-2-Methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)ethyl]amine;

N-Methyl-2-({3-[2-({3-[(2*R*)-2-methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)ethanamine;

2-{2-[2-2-(Dimethylamino)ethoxy]pyridin-3-yl}oxy}ethoxy}-3-[(2*R*)-2,4-

10 dimethylpiperazin-1-yl]pyrazine;

2-[2-({3-[2-2-(Dimethylamino)ethoxy]phenoxy)ethoxy]-3-[(2*R*)-2-methylpiperazin-1-yl]pyrazine;

{2-[2-({3-[2-({3-[(2*R*)-2-Methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)ethoxy}ethyl} amine

15 [6-({3-[2-({3-[(2*R*)-2-Methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)hexyl]amine;

[5-({3-[2-({3-[(2*R*)-2-Methylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)pentyl]amine

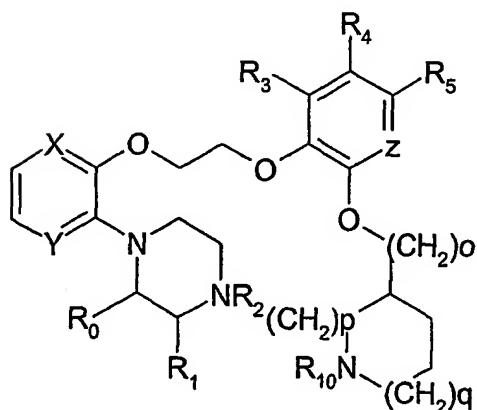
5-({3-[2-({3-[(2*R*)-2,4-Dimethylpiperazin-1-yl]pyrazin-2-yl}oxy)ethoxy]pyridin-2-yl}oxy)-

20 *N,N*-dimethylpentan-1-amine; or

2-[(2*R*)-2-Methylpiperazin-1-yl]-3-(2-({2-(2-piperazin-1-ylethoxy)pyridin-3-yl}oxy)ethoxy)pyrazine.

14. The compound according to any one of claims 1 to 9, which has the Formula (Ib):

25



Formula (Ib)

wherein:

 R_0 - R_5 , X, Y, and Z are as in any one of claims 1 to 8,

5 o is an integer 0-2;

p is an integer 0-2, wherein o and p are preferably not both 0;

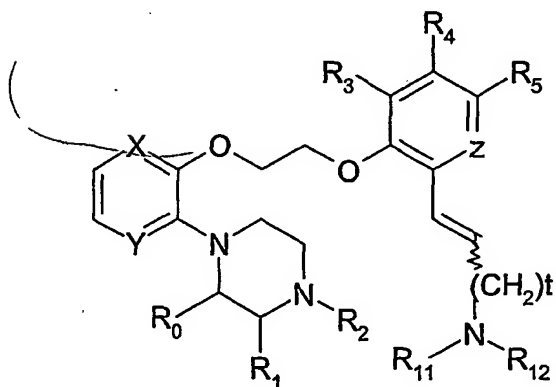
q is an integer 0-1;

 R_{10} is H or C_1 - C_4 -alkyl, preferably H or methyl.

10 15. The compound according to claim 14, which compound is:

2-[(2*R*)-2-Methylpiperazin-1-yl]-3-[2-({2-[(1-methylpiperidin-4-yl)oxy]pyridin-3-yl}oxy)ethoxy]pyrazine, trifluoroacetate;2-[(2*R*)-2-Methylpiperazin-1-yl]-3-[2-({2-[2-(1-methylpyrrolidin-2-yl)ethoxy]pyridin-3-yl}oxy)ethoxy]pyrazine, trifluoroacetate;15 2-[(2*R*)-2-Methylpiperazin-1-yl]-3-(2-{[2-(piperidin-3-ylmethoxy)pyridin-3-yl]oxy}ethoxy)pyrazine, trifluoroacetate;2-[(2*R*)-2-Methylpiperazin-1-yl]-3-{2-([2-({[(2*S*)-1-methylpyrrolidin-2-yl]methoxy}pyridin-3-yl)oxy]ethoxy}pyrazine, trifluoroacetate.

20 16. The compound according to any one of claims 1 to 9, which has the Formula (Ic):



Formula (Ic)

25 wherein:

 R_0 - R_5 , X, Y, and Z are as defined above,

t is an integer 1-11, preferably 1-8, more preferably 1-6; most preferably 1,

the orientation around the double bond may be either *cis* or *trans*;

R_{11} and R_{12} are each independently H or straight or branched C_1 - C_4 -alkyl; or R_{11} and R_{12} form together with the nitrogen atom to which they are attached a saturated heterocyclic ring.

5

17. The compound according to claim 16, wherein R_{11} and R_{12} are both methyl.

18. The compound according to any one of claims 16 or 17, which compound is:

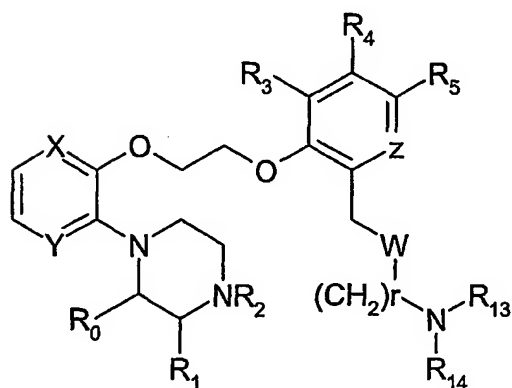
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2-{2-[2-[(1*Z*)-3-(Dimethylamino)prop-1-enyl]pyridin-3-yl]oxy}ethoxy}-3-[(2*R*)-2-methylpiperazin-1-yl]pyrazine; or

2-{2-[2-[(1*E*)-3-(Dimethylamino)prop-1-enyl]pyridin-3-yl]oxy}ethoxy}-3-[(2*R*)-2-methylpiperazin-1-yl]pyrazine.

19. The compound according to any one of claims 1 to 9, which has the Formula (Id):

15



Formula (Id)

wherein:

20 R_0 - R_5 , X, Y, and Z are as defined above,

W is O or CH_2 ;

r is 1-11, preferably 1-8, more preferably 1-6, most preferably 1 when W is CH_2 and most preferably 2 when W is O;

25 R_{13} and R_{14} are each independently H or straight or branched C_1 - C_4 -alkyl; or R_{13} and R_{14} form together with the nitrogen atom to which they are attached a saturated heterocyclic ring.

20. The compound according to claim 19, wherein W is O, X = N, and Y = N.

21. The compound according to claim 19, wherein $r = t$, $W = CH_2$, $X = N$, $Y = N$, $R_{13} = R_{11}$ and $R_{14} = R_{12}$; where t , R_{11} and R_{12} are as defined for formula (Ic) in claim 16

22. The compound according to any of claims 19 to 21, wherein R_{13} and R_{14} are both methyl.

23. The compound according to any one of claims 19 to 22, which compound is:
2-{2-[(2-{[2-(Dimethylamino)ethoxy]methyl}pyridin-3-yl)oxy]ethoxy}-3-[(2R)-2-methylpiperazin-1-yl]pyrazine; or
2-{2-[(2-{[3-(Dimethylamino)propyl]pyridin-3-yl)oxy]ethoxy}-3-[(2R)-2-methylpiperazin-1-yl]pyrazine.

24. The compound according to any one of claims 1 to 23 or use in therapy of a human being or an animal.

25. The compound according to claim 24 wherein the therapy is directed towards treatment of a serotonin-related disorder or condition related to the 5-HT_{2C} receptor.

26. The compound according to claim 25, wherein the serotonin-related disorder or condition is selected from memory disorders, such as Alzheimer's disease; schizophrenia; mood disorders such as depression; anxiety disorders; pain; substance abuse; sexual dysfunctions such as erectile dysfunction; epilepsy; glaucoma; urinary disorders, such as urinary incontinence; menopausal and post-menopausal hot flushes; type 2 diabetes; eating disorders, such as binge eating disorders, anorexia nervosa and bulimia; weight gain associated with antipsychotic drug administration, premenstrual tension, sleep disorders; and particularly obesity.

27. Use of a compound according to any one of claims 1 to 23 for the manufacture of a medicament for treating or preventing a serotonin-related disorder or condition related to the 5-HT_{2C} receptor.

28. The use according to claim 27, wherein the serotonin-related disorder or condition is selected from memory disorders including Alzheimer's disease; schizophrenia; mood disorders such as depression; anxiety disorders; pain; substance abuse; sexual dysfunctions such as erectile dysfunction; epilepsy; glaucoma; urinary disorders, such as urinary incontinence; menopausal and post-menopausal hot flushes; type 2 diabetes; eating disorders, such as binge eating disorders, anorexia nervosa and bulimia; weight gain associated with antipsychotic drug administration, premenstrual tension, sleep disorders; and particularly obesity.

29. A pharmaceutical composition comprising a compound according to any one of claims 1 to 23 as an active ingredient, together with a pharmaceutically acceptable carrier.

30. A method for the treatment of a serotonin-related disorder or condition, particularly 5-HT_{2C} receptor related, comprising administering to a subject in need thereof an effective amount of a compound according to any of claims 1 to 23.

31. The method according to claim 30, wherein the serotonin-related disorder or condition is selected from memory disorders including Alzheimer's disease; schizophrenia; mood disorders such as depression; anxiety disorders; pain; substance abuse; sexual dysfunctions such as erectile dysfunction; epilepsy; glaucoma; urinary disorders, such as urinary incontinence; menopausal and post-menopausal hot flushes; type 2 diabetes; eating disorders, such as binge eating disorders, anorexia nervosa and bulimia; weight gain associated with antipsychotic drug administration, premenstrual tension, sleep disorders; and particularly obesity.

32. The method according to any of claims 30 or 31, wherein the subject is a human.

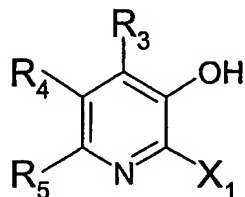
33. The method according to any of claims 30 or 31, wherein the subject is an animal.

34. A method for modulating 5-HT_{2C} receptor function, comprising contacting the receptor with an effective stimulatory or inhibitory, preferably stimulatory, amount of a compound according to any of claims 1 to 23.

35. A process for the preparation of a compound of the Formula (Ia) according to any one of claims 10 to 13, which process comprises:

a) reacting a compound of Formula (II)

5



Formula (II)

wherein:

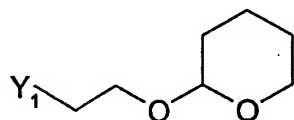
10 X_1 is selected from F, Cl, Br and I,

R_3 - R_5 are each independently H, halogen, methyl or methoxy, provided that at least one of R_3 -

R_5 is hydrogen,

with a compound of Formula (III):

15



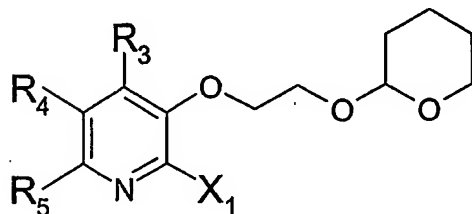
Formula (III)

wherein Y_1 is a suitable leaving group selected from Cl, Br, I, OTs, or OMs;

in the presence of a base, such as potassium carbonate, triethylamine, or pyridine, in a solvent

20 such as acetonitrile,

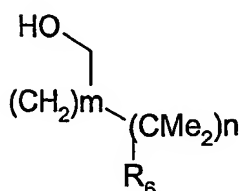
to give a compound of Formula (IV):



Formula (IV)

wherein X_1 and R_3 - R_5 are as defined above;

- b) reacting the compound of Formula (IV) with a compound of Formula (Va) in the presence
 5 of a base, such as potassium tert-butoxide, in a solvent, such as toluene,



Formula (Va)

10 wherein:

m is an integer 0-10, preferably 0-7, more preferably 0-5,

n is an integer 0 or 1, wherein the sum of $m+n$ is preferably at least 1,

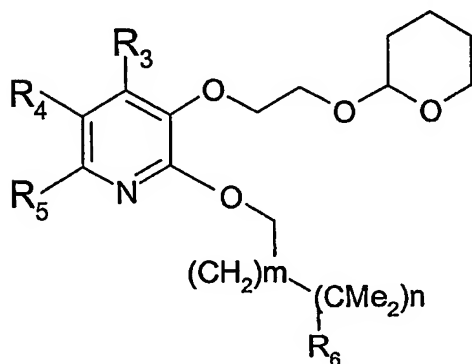
R_6 is NR_7R_8 or OR_9 , wherein

R_7 and R_8 are each independently H or straight or branched C_1 - C_4 -alkyl;

- 15 or R_7 and R_8 form together with the nitrogen atom to which they are attached a saturated heterocyclic ring;

R_9 is amino- C_2 - C_4 -alkyl or N,N-di- C_1 - C_4 -alkylamino- C_2 - C_4 -alkyl,

to give a compound of Formula (VIa):



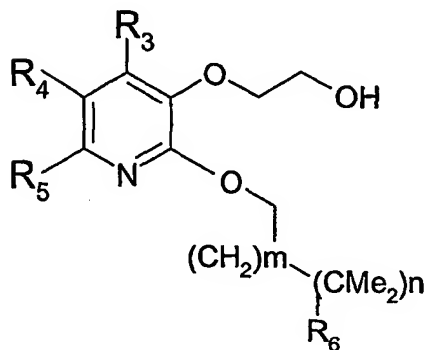
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Formula (VIa)

wherein:

R_3 - R_6 , m , and n are as defined above,

c) treating the compound of Formula (VIa) with an aqueous acid such as aqueous acetic acid or aqueous hydrochloric acid, to give a compound of Formula (VIIa):

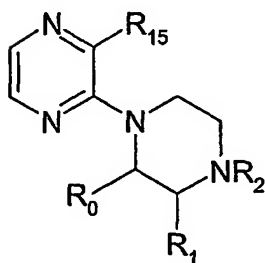


Formula (VIIa)

wherein:

R₃-R₆, m, and n are as defined above,

d) reacting the compound of Formula (VIIa) with a compound of Formula (VIII) in the presence of a base, such as potassium tert-butoxide, in a solvent, such as methyl tert-butyl ether or toluene,



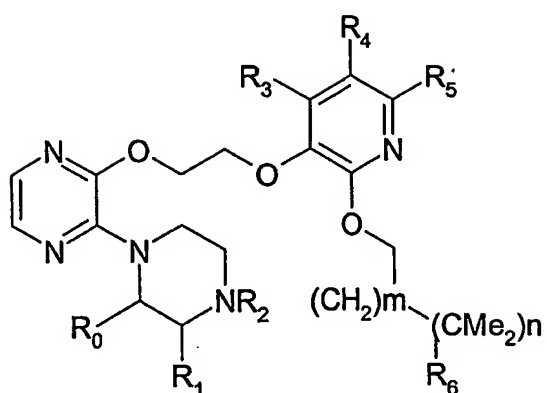
Formula (VIII)

wherein

R₀ and R₁ are each independently H or CH₃;

R₂ is selected from C₁-C₄-alkoxycarbonyl, benzyl, trityl, C₁-C₄-alkyl, 2-hydroxyethyl, 2-cyanoethyl, tetrahydropyran-2-yl, and C₁-C₄-acyl,

R₁₅ is halogen, such as chlorine, to give a compound of Formula (Ia) wherein X = N and Y = N:



Formula (Ia)

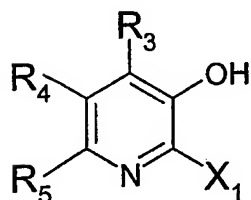
5 wherein R_0 - R_6 , m , and n are as defined above;

e) if desired, separating a racemate obtained into optical isomers and/or forming an acid addition salt with an organic or inorganic acid,

10 f) if R_2 in Formula (Ia) following step d) is a nitrogen protecting group, such as *t*-BOC, trityl, and benzyl, removing said nitrogen protecting group, such as under acidic conditions (e.g. trifluoroacetic acid in a solvent such as chloroform), hydrogenolytic or non-hydrogenolytic conditions, to provide the compound of Formula (Ia), wherein R_2 is hydrogen.

15 36. A process for the preparation of a compound of the Formula (Ib) according to any one of claims 14 or 15, which process comprises:

a) reacting a compound of Formula (II)



Formula (II)

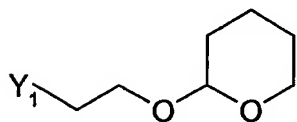
wherein:

X_1 is selected from F, Cl, Br and I,

R_3 - R_5 are each independently H, halogen, methyl or methoxy, provided that at least one of R_3 - R_5 is hydrogen,

with a compound of Formula (III):

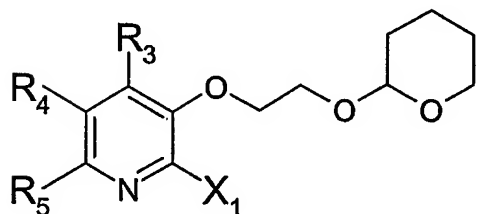
5



Formula (III)

wherein Y_1 is a suitable leaving group selected from Cl, Br, I, OTs, or OMs;

10 in the presence of a base, such as potassium carbonate, triethylamine, or pyridine, in a solvent, such as acetonitrile, to give a compound of Formula (IV):

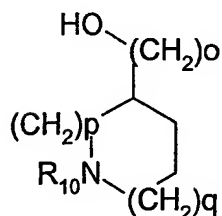


15 Formula (IV)

wherein X_1 and R_3 - R_5 are as defined above;

b) reacting the compound of Formula (IV) with a compound of Formula (Vb) in the presence of a base, such as potassium tert-butoxide, in a solvent, such as toluene,

20



Formula (Vb)

wherein:

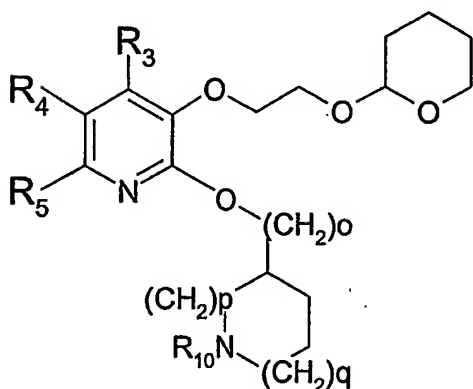
o is an integer 0-2;

p is an integer 0-2, wherein o and p are preferably not both 0;

q is an integer 0-1;

R₁₀ is H or C₁-C₄-alkyl, preferably H or methyl;

5 to give a compound of Formula (VIb):



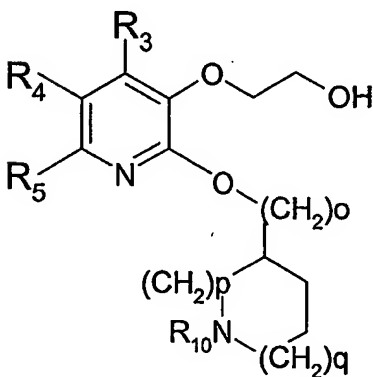
Formula (VIb)

10 wherein:

R₃-R₅ and R₁₀, o, p, and q are as defined above,

c) treating the compound of Formula (VIb) with an aqueous acid such as aqueous acetic acid or aqueous hydrochloric acid, to give a compound of Formula (VIIb):

15



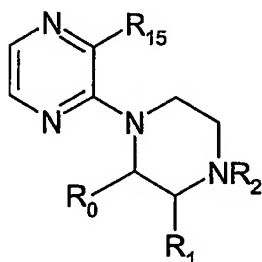
Formula (VIIb)

wherein:

20 R₃-R₅ and R₁₀, o, p, and q are as defined above,

d) reacting the compound of Formula (VIIb) with a compound of Formula (VIII) in the presence of a base such as potassium tert-butoxide, in a solvent, such as methyl tert-butyl ether or toluene,

5



Formula (VIII)

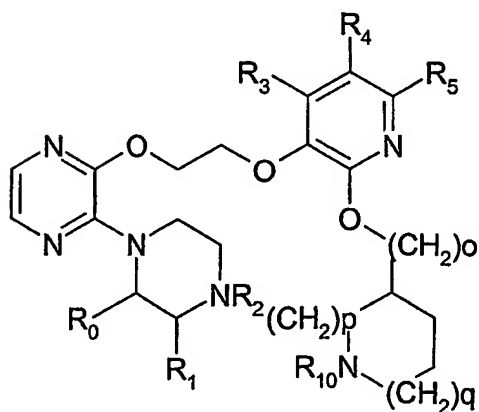
wherein

10 R_0 and R_1 are each independently H or CH_3 ;

R_2 is selected from C_1 - C_4 -alkoxycarbonyl, benzyl, trityl, C_1 - C_4 -alkyl, 2-hydroxyethyl, 2-cyanoethyl, tetrahydropyran-2-yl, and C_1 - C_4 -acyl,

R_{15} is halogen, such as chlorine, to give a compound of Formula (Ib) wherein $X = N$ and $Y = N$:

15



Formula (Ib)

wherein R_0 - R_5 , R_{10} , o , p , and q are as defined above;

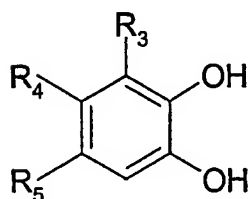
20

e) if desired, separating a racemate obtained into optical isomers and/or forming an acid addition salt with an organic or inorganic acid,

f) if R_2 in Formula (Ib) following step d) is a nitrogen protecting group, such as *t*-BOC, trityl, and benzyl, removing said nitrogen protecting group, such as under acidic conditions (e.g. trifluoroacetic acid in a solvent such as chloroform), hydrogenolytic or non-hydrogenolytic conditions, to provide the compound of Formula (Ib), wherein R_2 is hydrogen.

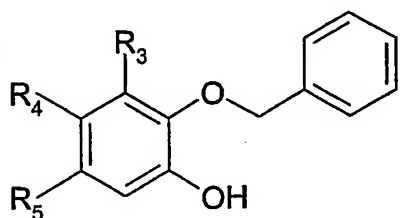
37. A process for the preparation of a compound of the Formula (Ia) according to any one of claims 10 to 13, which process comprises:

- 10 a) reacting a compound of Formula (IX) with a benzylating agent, such as benzyl chloride, benzyl bromide, or benzyl tosylate, in the presence of a base:



- 15 Formula (IX)

wherein R_3 - R_5 are each independently H, halogen, methyl, or methoxy, provided that at least one of R_3 - R_5 is hydrogen, to give a compound of Formula (X):

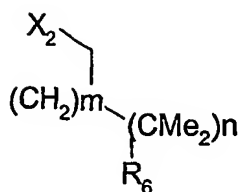


20

Formula (X)

wherein R_3 - R_5 are as defined above,

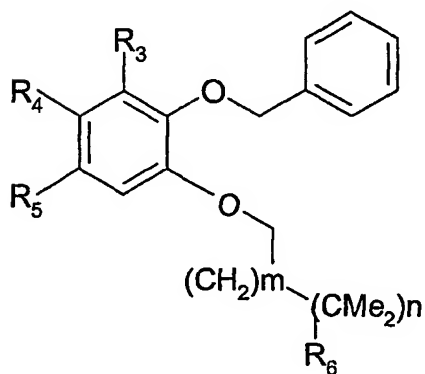
- 25 b) reacting the compound of Formula (X) with a compound of Formula (XIa) in the presence of a base, such as potassium carbonate, in a solvent, such as acetone:



Formula (XIa)

wherein

- 5 X_2 is halogen, OMs, or OTs;
 m is an integer 0-10, preferably 0-7, more preferably 0-5,
 n is an integer 0 or 1, wherein the sum of $m+n$ is preferably at least 1,
 R_6 is NR_7R_8 or OR_9 , wherein
 R_7 and R_8 are each independently H or straight or branched $\text{C}_1\text{-C}_4$ -alkyl;
 10 or R_7 and R_8 form together with the nitrogen atom to which they are attached a saturated heterocyclic ring;
 R_9 is amino- $\text{C}_2\text{-C}_4$ -alkyl or $\text{N,N-di-C}_1\text{-C}_4$ -alkylamino- $\text{C}_2\text{-C}_4$ -alkyl,
 to give a compound of Formula (XIIa):

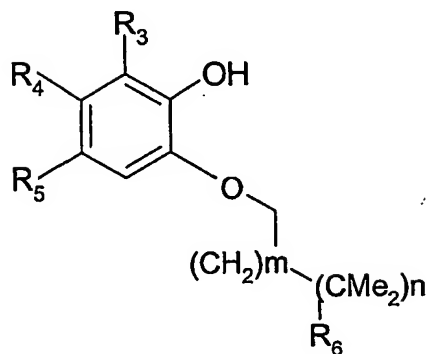


Formula (XIIa)

wherein

$\text{R}_3\text{-R}_6$, m , and n are as defined above;

20 c) treating the compound of Formula (XIIa) with hydrogen in the presence of a hydrogenation catalyst, such as palladium on carbon, in a solvent, such as methanol, to give a compound of Formula (XIIIa):

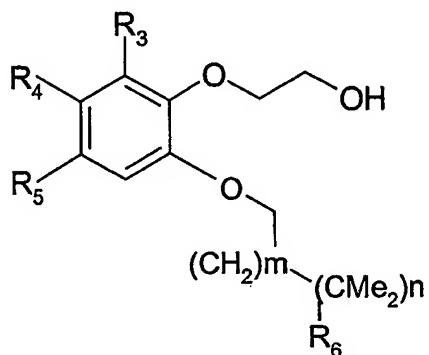


Formula (XIIIa)

wherein R_3 - R_6 , m , and n are as defined above;

5

d) reacting the compound of Formula (XIIIa) with a hydroxyethylating agent such as ethylene carbonate in the presence of a base, such as potassium carbonate, in a solvent, such as N,N-dimethylformamide, to give a compound of Formula (XIVa):

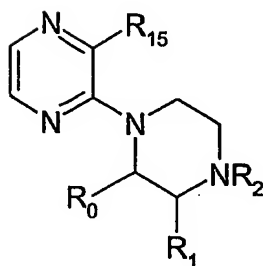


10

Formula (XIVa)

wherein R_3 - R_6 , m , and n are as defined above;

15 e) reacting the compound of Formula (XIVa) with a compound of Formula (VIII) in the presence of a base such as potassium tert-butoxide, in a solvent, such as N,N-dimethylformamide:

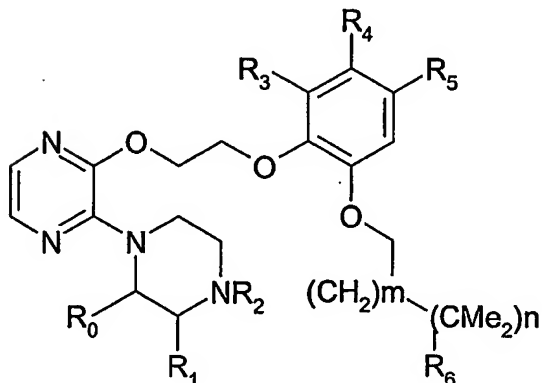


Formula (VIII)

wherein

- 5 R_0 and R_1 are each independently H or CH_3 ;
 R_2 is selected from C_1 - C_4 -alkoxycarbonyl, benzyl, trityl, C_1 - C_4 -alkyl, 2-hydroxyethyl, 2-cyanoethyl, tetrahydropyran-2-yl, and C_1 - C_4 -acyl,
 R_{15} is halogen, such as chlorine, to give a compound of Formula (Ia) wherein $X = N$ and $Y = N$:

10



Formula (Ia)

wherein R_0 - R_6 , m , and n are as defined above;

15

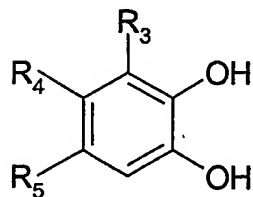
f) if desired, separating a racemate obtained into optical isomers and/or forming an acid addition salt with an organic or inorganic acid,

- g) if R_2 in Formula (Ia) following step e) is a nitrogen protecting group, such as *t*-BOC, trityl, and benzyl, removing said nitrogen protecting group, such as under acidic conditions (e.g. trifluoroacetic acid in a solvent such as chloroform), hydrogenolytic or non-hydrogenolytic conditions, to provide the compound of Formula (Ia), wherein R_2 is hydrogen.

20

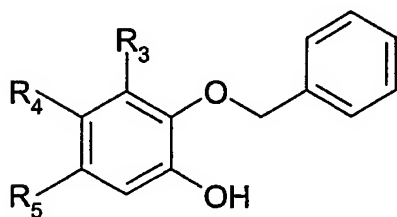
38. A process for the preparation of a compound of the Formula (Ib) according to any one of claims 14 or 15, which process comprises:

- 5 a) reacting a compound of Formula (IX) with a benzylating agent, such as benzyl chloride, benzyl bromide, or benzyl tosylate, in the presence of a base:



10 Formula (IX)

wherein R₃-R₅ are each independently H, halogen, methyl, or methoxy, provided that at least one of R₃-R₅ is hydrogen, to give a compound of Formula (X):

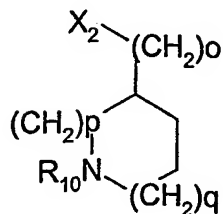


15

Formula (X)

wherein R₃-R₅ are as defined above,

- b) reacting the compound of Formula (X) with a compound of Formula (XIb) in the presence
20 of a base, such as potassium carbonate, in a solvent, such as acetone:



Formula (XIb)

wherein:

X₂ is halogen, OMs, or OTs;

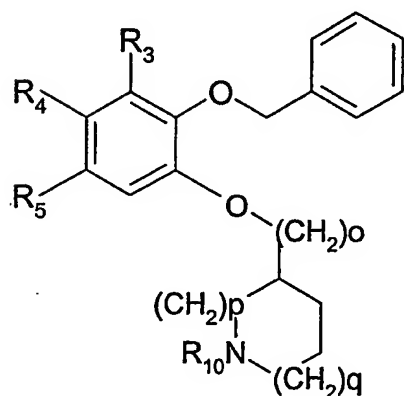
o is an integer 0-2;

5 p is an integer 0-2, wherein o and p are preferably not both 0;

q is an integer 0-1;

R₁₀ is H or C₁-C₄-alkyl, preferably H or methyl;

to give a compound of Formula (XIb):



10

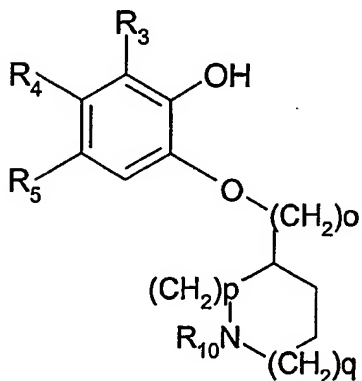
Formula (XIIb):

wherein:

R₃-R₅, R₁₀, o, p, and q are as defined above,

15

c) treating the compound of Formula (XIIb) with hydrogen in the presence of a hydrogenation catalyst, such as palladium on carbon, in a solvent, such as methanol, to give a compound of Formula (XIIIb):



20

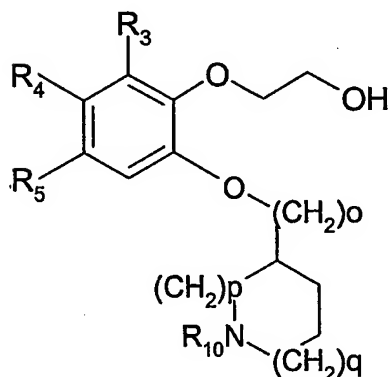
Formula (XIIIb):

wherein:

R_3 - R_5 , R_{10} , o, p, and q are as defined above,

5

d) reacting the compound of Formula (XIIIb) with a hydroxyethylating agent such as ethylene carbonate in the presence of a base, such as potassium carbonate, in a solvent, such as N,N-dimethylformamide, to give a compound of Formula (XIVb):



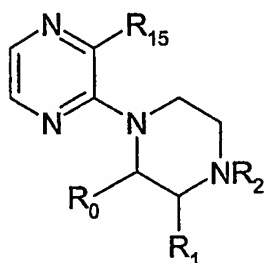
10

Formula (XIVb)

wherein R_3 - R_5 , R_{10} , o, p, and q are as defined above;

15

e) reacting the compound of Formula (XIVa) with a compound of Formula (VIII) in the presence of a base, such as potassium tert-butoxide, in a solvent, such as N,N-dimethylformamide:



20

Formula (VIII)

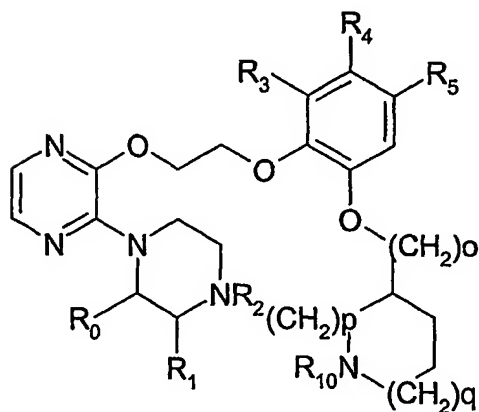
wherein

R_0 and R_1 are each independently H or CH_3 ;

R_2 is selected from C_1 - C_4 -alkoxycarbonyl, benzyl, trityl, C_1 - C_4 -alkyl, 2-hydroxyethyl, 2-cyanoethyl, tetrahydropyran-2-yl, and C_1 - C_4 -acyl,

R_{15} is halogen, such as chlorine, to give a compound of Formula (Ib) wherein $X = \text{N}$ and $Y =$

5 N:



Formula (Ib)

wherein R_0 - R_5 , R_{10} , o , p , and q are as defined above;

10

f) if desired, separating a racemate obtained into optical isomers and/or forming an acid addition salt with an organic or inorganic acid,

15

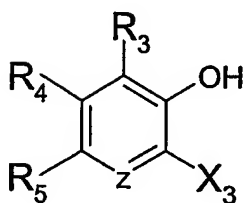
g) if R_2 in Formula (Ib) following step e) is a nitrogen protecting group, such as *t*-BOC, trityl, and benzyl, removing said nitrogen protecting group, such as under acidic conditions (e.g. trifluoroacetic acid in a solvent such as chloroform), hydrogenolytic or non-hydrogenolytic conditions, to provide the compound of Formula (Ib), wherein R_2 is hydrogen.

20

39. A process for the preparation of a compound of the Formula (Ia) according to any one of claims 10 to 13, which process comprises:

a) reacting a compound of Formula (XV) with a compound selected from benzyl chloride, benzyl bromide, benzyl iodide, benzyl tosylate, and benzyl mesylate in the presence of a base, such as potassium carbonate, in a solvent, such as *N,N*-dimethylformamide,

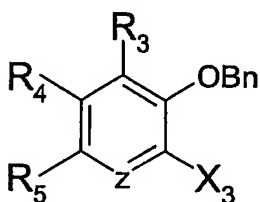
25



Formula (XV)

wherein:

- 5 X_3 is selected from Cl, Br and I, Z is CH or N,
 R_3 - R_5 are each independently H, halogen, methyl or methoxy, provided that at least one of R_3 - R_5 is hydrogen, to give a compound of Formula (XVI):

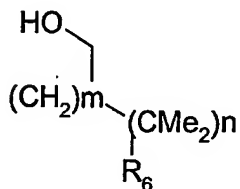


10

Formula (XVI)

wherein R_3 - R_5 , X_3 , and Z are as defined above;

- b) reacting the compound of Formula (XVI) with a compound of Formula (Va) in the
 15 presence of a base, such as sodium tert-butoxide, in a solvent, such as N,N-dimethylformamide,



20 Formula (Va)

wherein:

m is an integer 0-10, preferably 0-7, more preferably 0-5,

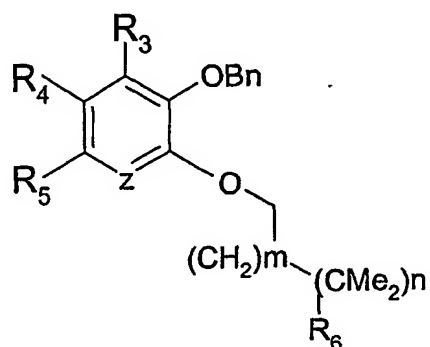
n is an integer 0 or 1, wherein the sum of m+n is preferably at least 1,

R_6 is NR_7R_8 or OR_9 , wherein

R_7 and R_8 are each independently H or straight or branched C_1 - C_4 -alkyl;
or R_7 and R_8 form together with the nitrogen atom to which they are attached a saturated heterocyclic ring;

R_9 is amino- C_2 - C_4 -alkyl or N,N-di- C_1 - C_4 -alkylamino- C_2 - C_4 -alkyl,

5 to give a compound of Formula (XVIIa):



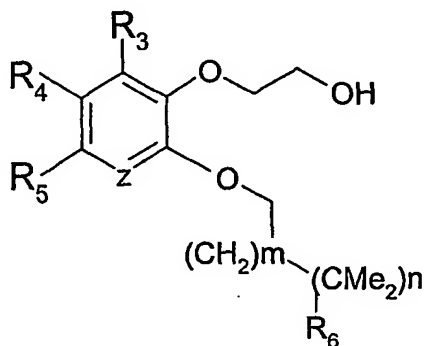
Formula (XVIIa)

10 wherein:

R_3 - R_6 , m , n , and Z are as defined above,

c) treating the compound of Formula (XVIIa) with a hydrogenation catalyst using a suitable hydrogen source such as ammonium formate and then heating in the presence of a

15 hydroxyethylating agent, preferably ethylene carbonate, and a base, such as potassium carbonate, in a solvent, such as N,N-dimethylformamide, to give a compound of Formula (VIIa):



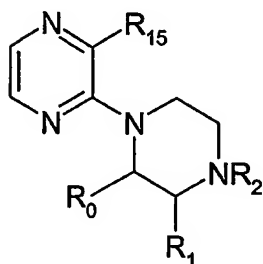
20

Formula (VIIa)

wherein:

R_3 - R_6 , m , n , and Z are as defined above,

- 5 d) reacting the compound of Formula (VIIa) with a compound of Formula (VIII) in the presence of a base, such as sodium tert-butoxide, in a solvent, such as N,N-dimethylformamide,



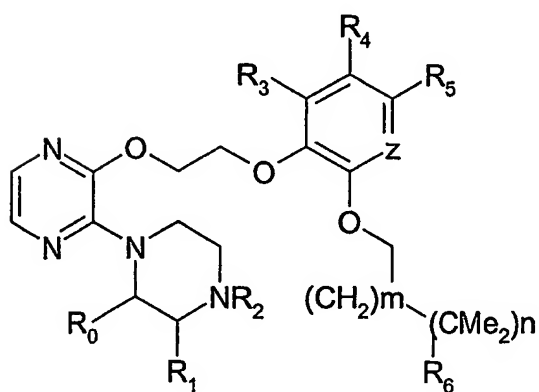
- 10 Formula (VIII)

wherein

R_0 and R_1 are each independently H or CH_3 ;

R_2 is selected from C_1 - C_4 -alkoxycarbonyl, benzyl, trityl, C_1 - C_4 -alkyl, 2-hydroxyethyl, 2-cyanoethyl, tetrahydropyran-2-yl, and C_1 - C_4 -acyl,

- 15 R_{15} is halogen, such as chlorine, to give a compound of Formula (Ia) wherein $X = N$ and $Y = N$:



- 20 Formula (Ia)

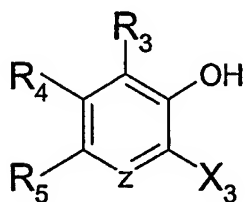
wherein R_0 - R_6 , m , n , and Z are as defined above;

e) if desired, separating a racemate obtained into optical isomers and/or forming an acid addition salt with an organic or inorganic acid,

f) if R_2 in Formula (Ia) following step d) is a nitrogen protecting group, such as *t*-BOC, trityl, and benzyl, removing said nitrogen protecting group, such as under acidic conditions (e.g. trifluoroacetic acid in a solvent such as chloroform), hydrogenolytic or non-hydrogenolytic conditions, to provide the compound of Formula (Ia), wherein R_2 is hydrogen.

40. A process for the preparation of a compound of the Formula (Ib) according to any one of claims 14 or 15, which process comprises:

a) reacting a compound of Formula (XV) with a compound selected from benzyl chloride, benzyl bromide, benzyl iodide, benzyl tosylate, and benzyl mesylate in the presence of a base, such as potassium carbonate, in a solvent, such as *N,N*-dimethylformamide,

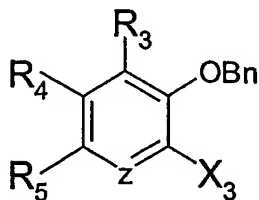


Formula (XV)

wherein:

X_1 is selected from Cl, Br and I, Z is CH or N,

R_3 - R_5 are each independently H, halogen, methyl or methoxy, provided that at least one of R_3 - R_5 is hydrogen, to give a compound of Formula (XVI):

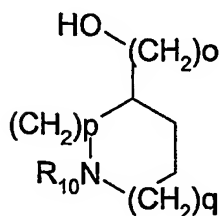


Formula (XVI)

wherein R_3 - R_5 , X_3 , and Z are as defined above;

b) reacting the compound of Formula (XVI) with a compound of Formula (Vb) in the presence of a base, such as sodium tert-butoxide, in a solvent, such as N,N-dimethylformamide,

5

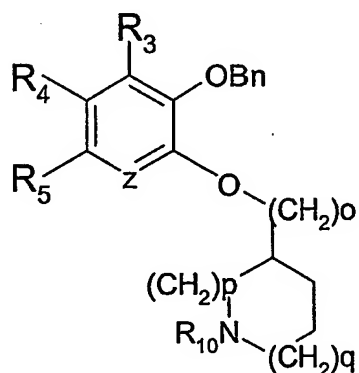


Formula (Vb)

wherein:

- 10 o is an integer 0-2;
 p is an integer 0-2, wherein o and p are preferably not both 0;
 q is an integer 0-1;
 R₁₀ is H or C₁-C₄-alkyl, preferably H or methyl;
 to give a compound of Formula (XVIIb):

15



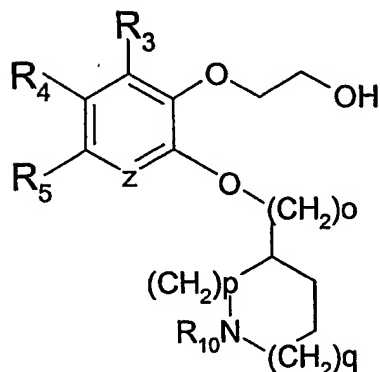
Formula (XVIIb)

wherein:

- 20 R₃-R₅ and R₁₀, o, p, q, and Z are as defined above,

c) treating the compound of Formula (XVIIb) with a hydrogenation catalyst using a suitable hydrogen source such as ammonium formate and then heating in the presence of a

hydroxyethylating agent, preferably ethylene carbonate, and a base, such as potassium carbonate, in a solvent, such as N,N-dimethylformamide, to give a compound of Formula (VIIb):

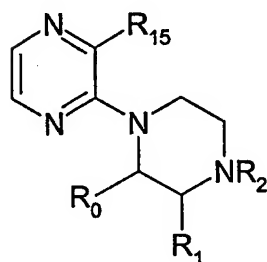


Formula (VIIb)

wherein:

R₃-R₅ and R₁₀, o, p, q, and Z are as defined above,

d) reacting the compound of Formula (VIIb) with a compound of Formula (VIII) in the presence of a base such as sodium tert-butoxide, in a solvent, such as N,N-dimethylformamide,



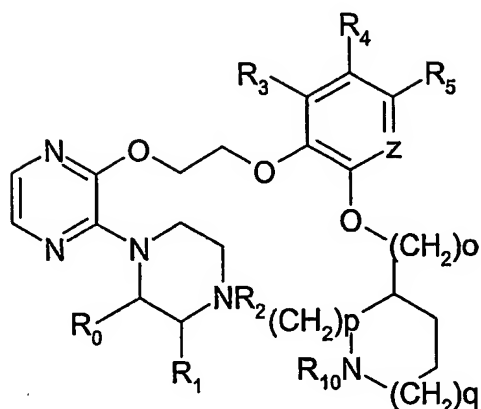
Formula (VIII)

wherein

R₀ and R₁ are each independently H or CH₃;

R₂ is selected from C₁-C₄-alkoxycarbonyl, benzyl, trityl, C₁-C₄-alkyl, 2-hydroxyethyl, 2-cyanoethyl, tetrahydropyran-2-yl, and C₁-C₄-acyl,

R_{15} is halogen, such as chlorine, to give a compound of Formula (Ib) wherein $X = N$ and $Y = N$:



5

Formula (Ib)

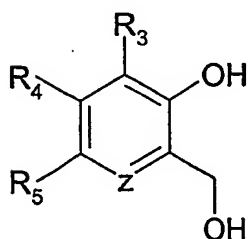
wherein R_0 - R_5 , R_{10} , o , p , q , and Z are as defined above;

- e) if desired, separating a racemate obtained into optical isomers and/or forming an acid addition salt with an organic or inorganic acid,
- f) if R_2 in Formula (Ib) following step d) is a nitrogen protecting group, such as *t*-BOC, trityl, and benzyl, removing said nitrogen protecting group, such as under acidic conditions (e.g. trifluoroacetic acid in a solvent such as chloroform), hydrogenolytic or non-hydrogenolytic conditions, to provide the compound of Formula (Ib), wherein R_2 is hydrogen.

15

41. A process for the preparation of a compound of the Formula (Ic) according to any one of claims 16 to 18, which process comprises:

- a) reacting a compound of formula (XVIII):



Formula (XVIII)

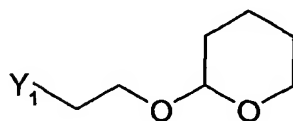
wherein:

R_3 - R_5 are each independently H, halogen, methyl or methoxy, provided that at least one of R_3 -

5 R_5 is hydrogen;

Z is CH or N,

with a compound of Formula (III):



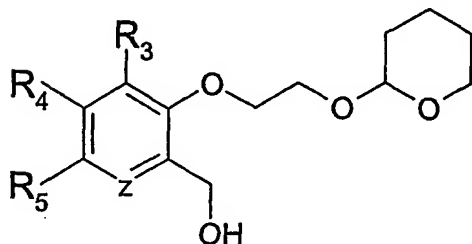
10

Formula (III)

wherein Y_1 is a suitable leaving group selected from Cl, Br, I, OTs, or OMs;

in the presence of a base, such as potassium carbonate, triethylamine, or pyridine, in a solvent, such as acetonitrile, to give a compound of Formula (XIX):

15

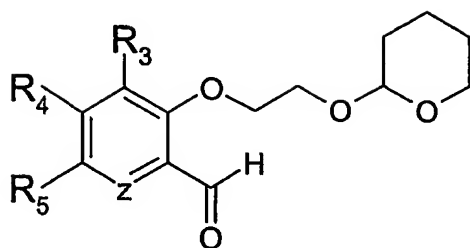


Formula (XIX)

wherein R_3 - R_5 and Z are as defined above,

20

b) transforming the alcohol function in the compound of Formula (XVI) into an aldehyde function with dimethyl sulfoxide and oxalyl chloride in dichloromethane, to give a compound of Formula (XX):



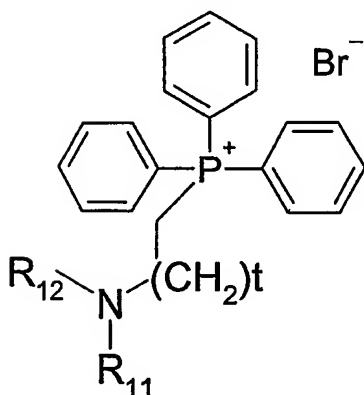
Formula (XX)

5 wherein:

R₃-R₅ and Z are as defined above,

c) reacting the compound of Formula (XX) with a compound of Formula (XXI) in the presence of a base, such as potassium tert-butoxide in a solvent mixture consisting of

10 tetrahydrofuran and tert-butanol,

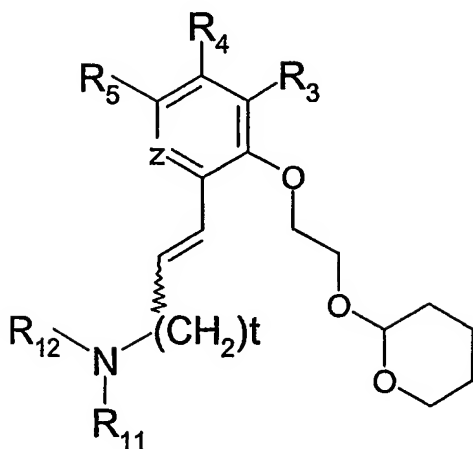


Formula (XXI)

15 wherein:

t is an integer 1-11, preferably 1-8, more preferably 1-6, most preferably 1; and

R₁₁ and R₁₂ are each independently H or straight or branched C₁-C₄-alkyl; or R₁₁ and R₁₂ form together with the nitrogen atom to which they are attached a saturated heterocyclic ring, to give a compound of Formula (XXII):



Formula (XXII)

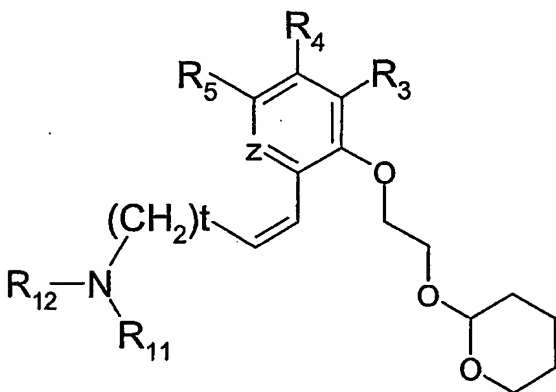
wherein:

- 5 R_3 - R_5 , R_{11} , R_{12} , t , and Z are as defined above;

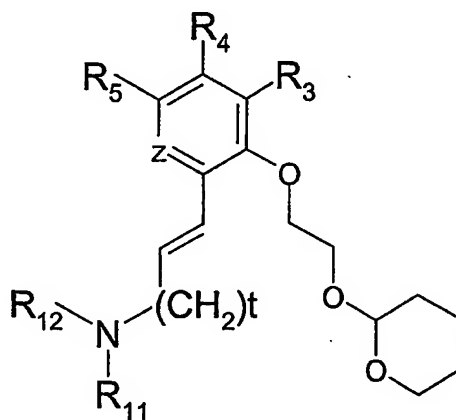
the orientation around the double bond may be either *cis* or *trans*;

d) separation by preparative HPLC and isolation of the *cis* and *trans* isomers of compound of Formula (XXII) to provide the individual *cis* isomer of Formula (XXIII) and the individual

- 10 *trans* isomer of Formula (XXIV)



Formula (XXIII)

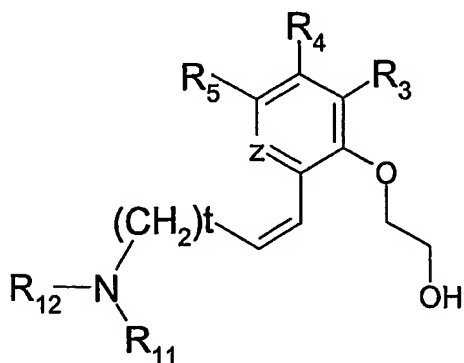


Formula (XXIV)

- 15 wherein:

R_3 - R_5 , R_{11} , R_{12} , t , and Z are as defined above;

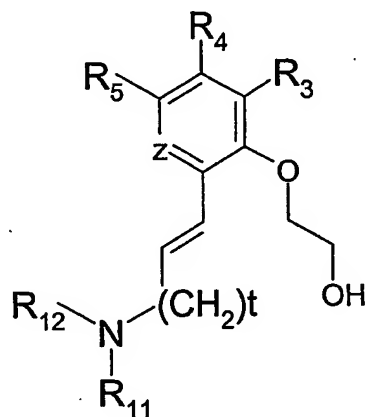
e) treating the compounds of Formula (XXIII) and (XXIV), respectively, with an aqueous acid such as aqueous acetic acid or aqueous hydrochloric acid, to give compounds of Formula (XXV) and (XXVI), respectively:



Formula (XXV)

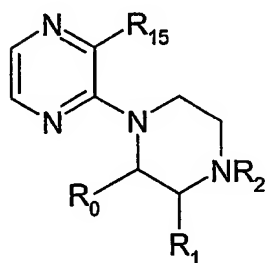
wherein:

R_3 - R_5 , R_{11} , R_{12} , t , and Z are as defined above;



Formula (XXVI)

f) reacting the compounds of Formula (XXV) and (XXVI) with a compound of Formula (VIII) in the presence of a base, such as potassium tert-butoxide, in a solvent, such as N,N-dimethylformamide:



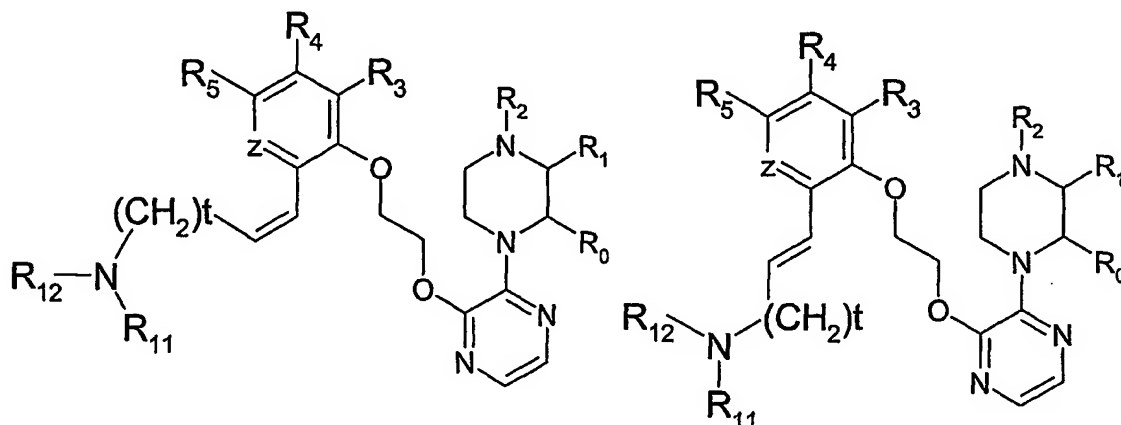
Formula (VIII)

wherein

R_0 and R_1 are each independently H or CH_3 ;

R_2 is selected from C_1 - C_4 -alkoxycarbonyl, benzyl, trityl, C_1 - C_4 -alkyl, 2-hydroxyethyl, 2-cyanoethyl, tetrahydropyran-2-yl, and C_1 - C_4 -acyl,

R₁₅ is halogen, such as chlorine, to give compounds of Formula (XXVII) and (XXVIII):



5 Formula (XXVII)

Formula (XXVIII)

wherein:

R₀-R₅, R₁₁, R₁₂, t, and Z are as defined above;

wherein the compounds of Formula (XXVII) and (XXVIII) are isomers of the compound of Formula (Ic) wherein X = N and Y = N;

10

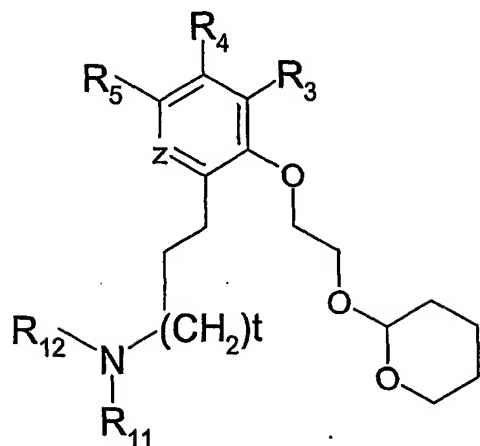
g) if R₂ in Formula (Ic) following step f) is a nitrogen protecting group, such as *t*-BOC, trityl, and benzyl, removing said nitrogen protecting group, such as under acidic conditions (e.g. trifluoroacetic acid in a solvent such as chloroform), hydrogenolytic or non-hydrogenolytic conditions, to provide the compound of Formula (Ic), wherein R₂ is hydrogen.

15

42. A process for the preparation of a compound of the Formula (Id) according to any one of claims 19 and 21 to 23, which process comprises:

a) treating the compound of Formula (XXII) with hydrogen in the presence of a hydrogen catalyst such palladium on carbon, in a solvent, such as methanol, to give a compound of Formula (XXIX):

20

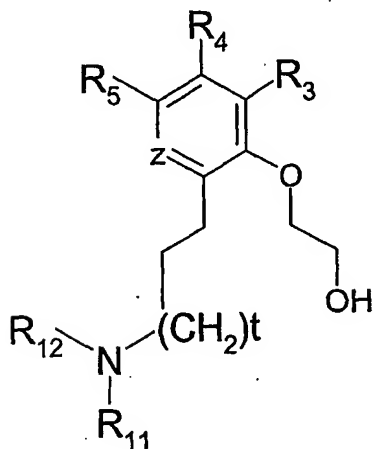


Formula (XXIX)

wherein:

- 5 R_3 - R_5 are each independently H, halogen, methyl, or methoxy, provided that at least one of R_3 - R_5 is hydrogen,
 Z is CH or N,
 t is an integer 1-11, preferably 1-8, more preferably 1-6, most preferably 1; and
 R_{11} and R_{12} are each independently H or straight or branched C_1 - C_4 -alkyl; or R_{11} and R_{12} form
 10 together with the nitrogen atom to which they are attached a saturated heterocyclic ring;

b) treating the compound of Formula (XXIX) with an aqueous acid such as aqueous acetic acid or aqueous hydrochloric acid, to give a compound of Formula (XXX):

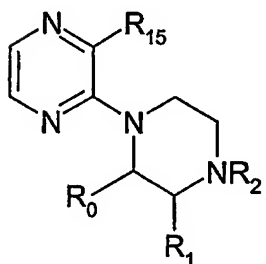


Formula (XXX)

wherein:

R_3 - R_5 , R_{11} , R_{12} , t , and Z are as defined above;

- 5 c) reacting the compound of Formula (XXX) with a compound of Formula (VIII) in the presence of a base, such as potassium tert-butoxide, in a solvent, such as N,N-dimethylformamide or dioxane:



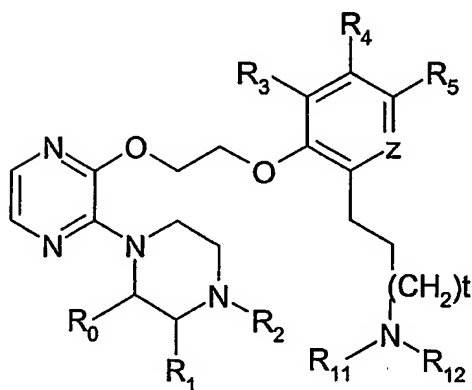
- 10 Formula (VIII)

wherein

R_0 and R_1 are each independently H or CH_3 ;

R_2 is selected from C_1 - C_4 -alkoxycarbonyl, benzyl, trityl, C_1 - C_4 -alkyl, 2-hydroxyethyl, 2-cyanoethyl, tetrahydropyran-2-yl, and C_1 - C_4 -acyl,

- 15 R_{15} is halogen, such as chlorine, to give a compound of Formula (XXXI):



Formula (XXXI):

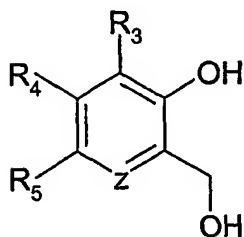
- 20 wherein:

R_0 - R_5 , R_{11} , R_{12} , t , and Z are as defined above; wherein Formula (XXXI) corresponds to Formula (Id) wherein $W = CH_2$, $r = t$, $X = N$, $Y = N$, $R_{13} = R_{11}$, and $R_{14} = R_{12}$,

- d) if R_2 in Formula (Id) following step c) is a nitrogen protecting group, such as *t*-BOC, trityl, and benzyl, removing said nitrogen protecting group, such as under acidic conditions (e.g. trifluoroacetic acid in a solvent such as chloroform), hydrogenolytic or non-hydrogenolytic
- 5 conditions, to provide the compound of Formula (Id), wherein R_2 is hydrogen.

43. A process for the preparation of a compound of the Formula (Id) according to any one of claims 19, 20, 22, or 23, which process comprises:

- 10 a) reacting a compound of Formula (XVIII):



Formula (XVIII)

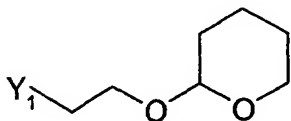
- 15 wherein:

R_3 - R_5 are each independently H, halogen, methyl or methoxy, provided that at least one of R_3 - R_5 is hydrogen;

Z is CH or N,

with a compound of Formula (III):

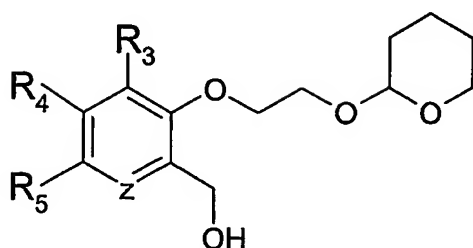
20



Formula (III)

wherein Y_1 is a suitable leaving group selected from Cl, Br, I, OTs, or OMs;

- 25 in the presence of a base, such as potassium carbonate, triethylamine, or pyridine, in a solvent, such as acetonitrile, to give a compound of Formula (XIX):

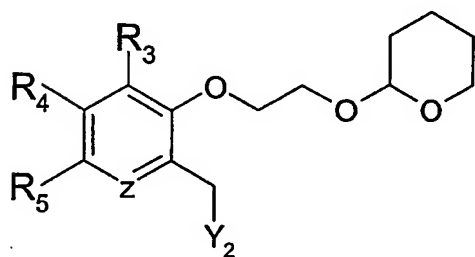


Formula (XIX)

wherein R_3 - R_5 and Z are as defined above,

5

b) transforming the alcohol function in Formula (XIX) into a suitable leaving group, e.g. by treatment with methanesulfonic anhydride in the presence of triethylamine in dichloromethane, to give a compound of Formula (XXXII):



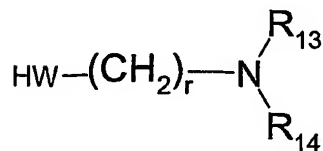
10

Formula (XXXII)

wherein R_3 - R_5 , and Z are as defined above;

Y_2 is halogen, OMs, or OTs;

15 c) reacting the compound of Formula (XXXII) with a compound of Formula (XXXIII) in the presence of a base, such as potassium tert-butoxide, in a solvent, such as dioxane:



20 Formula (XXXIII)

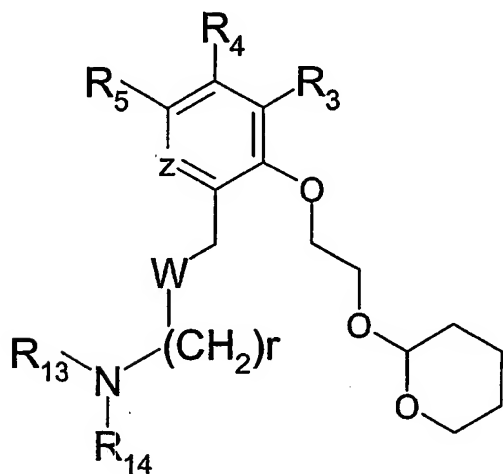
wherein:

W is O;

r is an integer of 1-11, preferably 1-8, more preferably 1-6, most preferably 2;

R₁₃ and R₁₄ are each independently H or straight or branched C₁-C₄-alkyl; or R₁₃ and R₁₄ form together with the nitrogen atom to which they are attached a saturated heterocyclic ring, to give a compound of Formula (XXXIV):

5

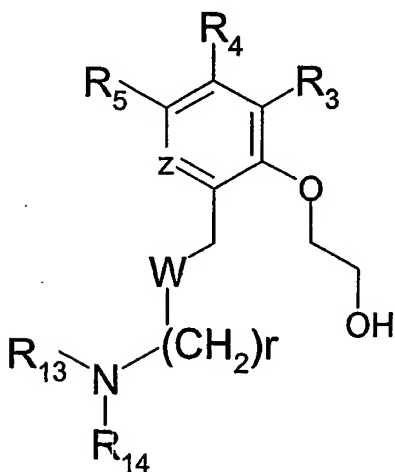


Formula (XXXIV)

wherein:

10 r, z, W, R₃-R₅, and R₁₃ and R₁₄ are as described above;

d) treating the compound of Formula (XXXIV) with an aqueous acid such as aqueous acetic acid or aqueous hydrochloric acid, to give a compound of Formula (XXXV):



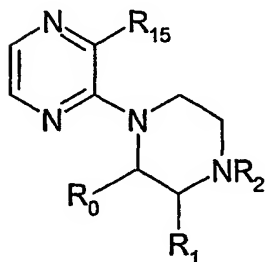
15

Formula (XXXV)

wherein:

r, z, W, R₃-R₅, and R₁₃ and R₁₄ are as described above;

- 5 e) reacting the compound of Formula (XXXV) with a compound of Formula (VIII) in the presence of a base, such as potassium tert-butoxide, in a solvent, such as N,N-dimethylformamide:



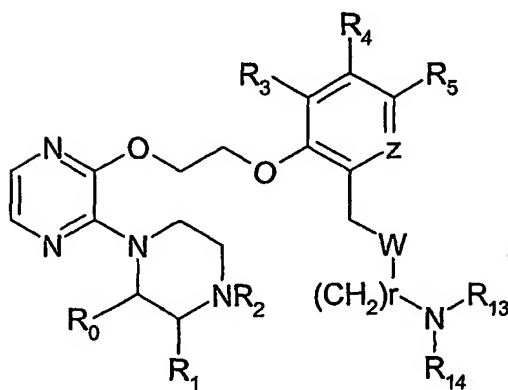
- 10 Formula (VIII)

wherein

R₀ and R₁ are each independently H or CH₃;

R₂ is selected from C₁-C₄-alkoxycarbonyl, benzyl, trityl, C₁-C₄-alkyl, 2-hydroxyethyl, 2-cyanoethyl, tetrahydropyran-2-yl, and C₁-C₄-acyl,

- 15 R₁₅ is halogen, such as chlorine, to give a compound of Formula (XXXVI):



Formula (XXXVI):

- 20 wherein:

R₀-R₅, R₁₃, R₁₄, r, W, and Z are as defined above; wherein Formula (XXXVI) corresponds to Formula (Id) wherein X = N and Y = N,

f) if R₂ in Formula (Id) following step e) is a nitrogen protecting group, such as *t*-BOC, trityl, and benzyl, removing said nitrogen protecting group, such as under acidic conditions (e.g. trifluoroacetic acid in a solvent such as chloroform), hydrogenolytic or non-hydrogenolytic
5 conditions, to provide the compound of Formula (Id), wherein R₂ is hydrogen.

44. A method for treating a disorder or condition, comprising administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 23, wherein the disorder or condition is selected from memory disorders including Alzheimer's
10 disease; schizophrenia; mood disorders such as depression; anxiety disorders; pain; substance abuse; sexual dysfunctions such as erectile dysfunction; epilepsy; glaucoma; urinary disorders, such as urinary incontinence; menopausal and post-menopausal hot flushes; type 2 diabetes; eating disorders, such as binge eating disorders, anorexia nervosa and bulimia; weight gain associated with antipsychotic drug administration, premenstrual tension, sleep
15 disorders; and particularly obesity.

45. Use of a compound according to any one of claims 1 to 23 for the manufacture of a medicament for treating or preventing memory disorders including Alzheimer's disease; schizophrenia; mood disorders such as depression; anxiety disorders; pain; substance abuse;
20 sexual dysfunctions such as erectile dysfunction; epilepsy; glaucoma; urinary disorders, such as urinary incontinence; menopausal and post-menopausal hot flushes; type 2 diabetes; eating disorders, such as binge eating disorders, anorexia nervosa and bulimia; weight gain associated with antipsychotic drug administration, premenstrual tension, sleep disorders; and particularly obesity.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 03/01044

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/14, C07D 401/12, C07D 401/04, C07D 401/08, C07D 403/04,
C07D 403/14, C07D 241/12, C07D 241/20, A61K 31/444, 31/497, A61P 25/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0076984 A2 (PHARMACIA & UPJOHN AB), 21 December 2000 (21.12.00) --	1-45
X	WO 0240457 A1 (BIOVITRUM AB), 23 May 2002 (23.05.02) --	1-45
X	WO 0240456 A1 (BIOVITRUM AB), 23 May 2002 (23.05.02) --	1-45
A	Journal of Medicinal Chemistry, Volume 21, no. 6, 1978, William C. Lumma et al: "Piperazinylpyrazines with Central Serotoninmimetic Activity", page 536 - page 542 --	1-45

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier application or patent but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

23 Sept. 2003

Date of mailing of the international search report

25-09-2003

Name and mailing address of the ISA/
 Swedish Patent Office
 Box 5055, S-102 42 STOCKHOLM
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Authorized officer

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 Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No..
PCT/SE 03/01044

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	<p>WO 03000663 A1 (PFIZER PRODUCTIONS INC.), 3 January 2003 (03.01.03)</p> <p style="text-align: center;">-- -----</p>	1-45

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/01044

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **30-34, 44**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/01044

Claims 30-34 and 44 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practiced on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for these (this) claim(s). The search has been based on the alleged effects of the compounds or compositions.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 03/01044

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	0076984	A2	21/12/00	AU	1428000 A	22/05/00
				AU	4969000 A	02/01/01
				BR	0010783 A	09/04/02
				CA	2374898 A	21/12/00
				CN	1360583 T	24/07/02
				EP	1140404 A	10/10/01
				EP	1178973 A	13/02/02
				JP	2002528280 T	03/09/02
				JP	2003502317 T	21/01/03
				NO	20015686 A	15/01/02
				SE	9901884 D	00/00/00
				US	6465467 B	15/10/02
				US	2003092694 A	15/05/03
WO	0240457	A1	23/05/02	AU	1529402 A	27/05/02
				SE	0004244 D	00/00/00
				US	2002103204 A	01/08/02
WO	0240456	A1	23/05/02	AU	2426602 A	27/05/02
				SE	0004245 D	00/00/00
				US	6593330 B	15/07/03
				US	2002147200 A	10/10/02
WO	03000663	A1	03/01/03	AP	200202561 D	00/00/00
				US	2003105106 A	05/06/03
				US	2003125334 A	03/07/03
				WO	03000666 A	03/01/03